



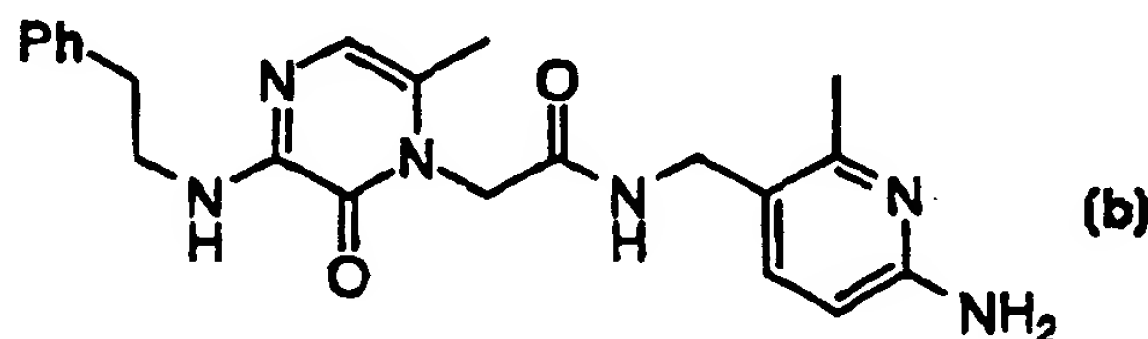
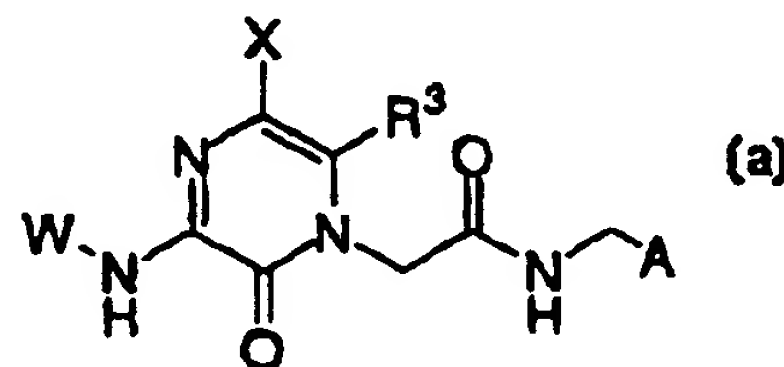
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

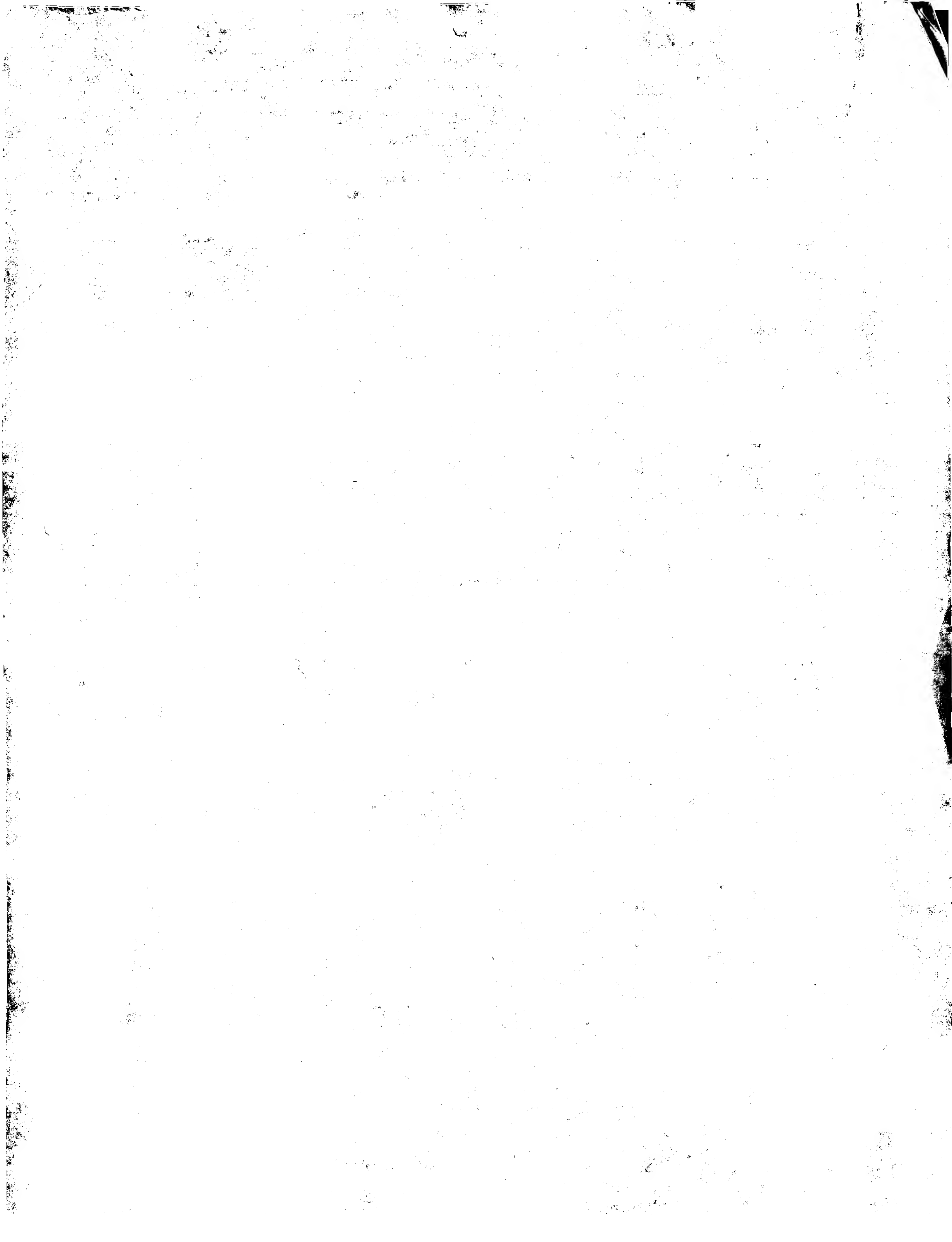
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(21) International Application Number: PCT/US97/06744 (22) International Filing Date: 18 April 1997 (18.04.97) (30) Priority Data: <table><tr><td>60/016,041</td><td>23 April 1996 (23.04.96)</td><td>US</td></tr><tr><td>9609714.2</td><td>9 May 1996 (09.05.96)</td><td>GB</td></tr><tr><td>60/043,009</td><td>14 April 1997 (14.04.97)</td><td>US</td></tr></table> (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): SANDERSON, Philip, E. [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). LYLE, Terry, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). DORSEY, Bruce, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). VAR-SOLONA, Richard, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			60/016,041	23 April 1996 (23.04.96)	US	9609714.2	9 May 1996 (09.05.96)	GB	60/043,009	14 April 1997 (14.04.97)	US	(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
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(54) Title: **PYRAZINONE THROMBIN INHIBITORS**

(57) Abstract

Compounds of the invention are useful in inhibiting thrombin and associated thrombotic occlusions having structure (a), for example (b).





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TITLE OF THE INVENTION

PYRAZINONE THROMBIN INHIBITORS

BACKGROUND OF THE INVENTION

5 Thrombin is a serine protease present in blood plasma in the form of a precursor, prothrombin. Thrombin plays a central role in the mechanism of blood coagulation by converting the solution plasma protein, fibrinogen, into insoluble fibrin.

 Edwards *et al.*, *J. Amer. Chem. Soc.*, (1992) vol. 114, pp.
10 1854-63, describes peptidyl α -ketobenzoxazoles which are reversible inhibitors of the serine proteases human leukocyte elastase and porcine pancreatic elastase.

 European Publication 363 284 describes analogs of peptidase substrates in which the nitrogen atom of the scissile amide group of the
15 substrate peptide has been replaced by hydrogen or a substituted carbonyl moiety.

 Australian Publication 86245677 also describes peptidase inhibitors having an activated electrophilic ketone moiety such as fluoromethylene ketone or α -keto carboxyl derivatives.

20 R. J. Brown *et al.*, *J. Med. Chem.*, Vol. 37, pages 1259-1261 (1994) describes orally active, non-peptidic inhibitors of human leukocyte elastase which contain trifluoromethylketone and pyridinone moieties.

 H. Mack *et al.*, *J. Enzyme Inhibition*, Vol. 9, pages 73-86
25 (1995) describes rigid amidino-phenylalanine thrombin inhibitors which contain a pyridinone moiety as a central core structure.

SUMMARY OF THE INVENTION

30 The invention includes a composition for inhibiting loss of blood platelets, inhibiting formation of blood platelet aggregates, inhibiting formation of fibrin, inhibiting thrombus formation, and inhibiting embolus formation in a mammal, comprising a compound of the invention in a pharmaceutically acceptable carrier. These compositions may optionally include anticoagulants, antiplatelet agents,

- 2 -

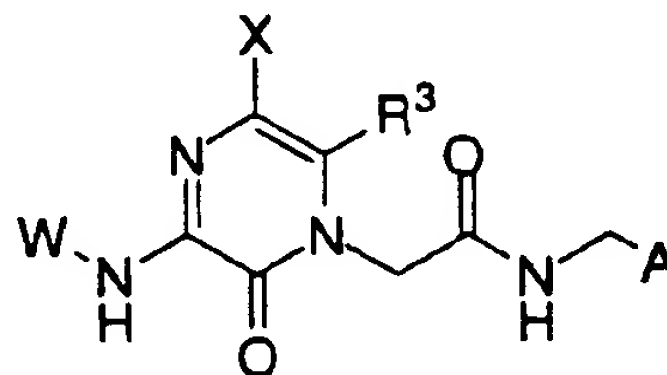
and thrombolytic agents. The compositions can be added to blood, blood products, or mammalian organs in order to effect the desired inhibitions.

The invention also includes a composition for preventing or treating unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels, in a mammal, comprising a compound of the invention in a pharmaceutically acceptable carrier. These compositions may optionally include anticoagulants, antiplatelet agents, and thrombolytic agents.

The invention also includes a method for reducing the thrombogenicity of a surface in a mammal by attaching to the surface, either covalently or noncovalently, a compound of the invention.

15 DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

Compounds of the invention are useful as thrombin inhibitors and have therapeutic value in for example, preventing coronary artery disease, and have the following structure:



wherein

W is

hydrogen,
R¹,
R¹OCO,
R¹CO,
R¹(CH₂)_nNHCO, or
(R¹)₂CH(CH₂)_nNHCO,

- 3 -

wherein n is 0-4;

R^1 is

- 5 R^2 ,
 $R^2(CH_2)_mC(R^{12})_2$, where m is 0-3, and each R^{12} can be the same
or different,
 $(R^2)(OR^2)CH(CH_2)_p$, where p is 1-4,
 $R^2C(R^{12})_2(CH_2)_m$, wherein m is 0-3, and each R^{12} can be the
10 same or different, wherein $(R^{12})_2$ can also form a ring with
C represented by C3-7 cycloalkyl,
 $R^2CH_2C(R^{12})_2(CH_2)_q$, wherein m is 0-2, and each R^{12} can be the
same or different, wherein $(R^{12})_2$ can also form a ring with
C represented by C3-7 cycloalkyl,
15 $(R^2)_2CH(CH_2)_r$, where r is 0-4 and each R^2 can be the same or
different, and wherein $(R^2)_2$ can also form a ring with CH
represented by C3-7 cycloalkyl, C7-12 bicyclic alkyl, C10-16
tricyclic alkyl, or a 5- to 7- membered mono- or bicyclic
heterocyclic ring which can be saturated or unsaturated, and
20 the group consisting of N, O and S,
 $R^2O(CH_2)_p$, wherein p is 1-4, or
 $R^2(COOR^3)(CH_2)_r$, where r is 1-4;

R^2 and R^{14} are independently

- 25 phenyl, unsubstituted or substituted with one or more of C1-4
alkyl, C1-4 alkoxy, halogen, hydroxy, COOH, CONH₂, or
SO₂NH₂,
naphthyl,
biphenyl,
30 a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
heterocyclic ring or non-heterocyclic ring which can be saturated
or unsaturated, wherein the heterocyclic ring contains from one to
four heteroatoms selected from the group consisting of N, O and

- 4 -

S, and wherein the heterocyclic or non-heterocyclic ring is unsubstituted or substituted with halogen or hydroxy, C₁-7 alkyl, unsubstituted or substituted with one or more of

hydroxy,
 5 COOH,
 amino,
 aryl,
 C₃-7 cycloalkyl,
 CF₃,
 10 N(CH₃)₂,
 -C₁-3alkylaryl,
 heteroaryl, or
 heterocycloalkyl,
 CF₃

15 C₃-7 cycloalkyl, unsubstituted or substituted with aryl,
 C₇-12 bicyclic alkyl, or
 C₁₀-16 tricyclic alkyl;

R³ is

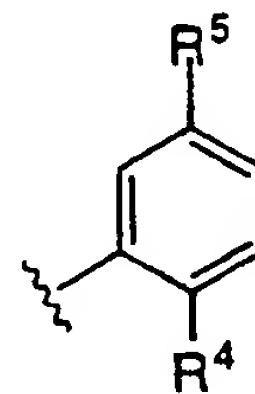
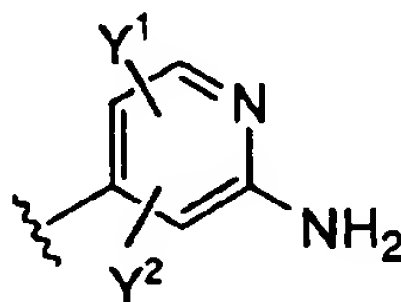
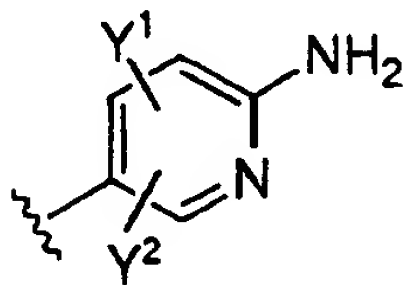
20 hydrogen,
 C₁-4 alkyl,
 C₃-7 cycloalkyl, or
 trifluoromethyl;

25 X is

hydrogen, or
 halogen;

A is chosen from one of the following radicals:

30



- 5 -

wherein Y¹ and Y² are independently

hydrogen,
C1-4 alkyl,
C1-4 alkoxy,
5 C3-7 cycloalkyl,
halogen, or
trifluoromethyl;

R⁴ is

10 hydrogen,
C1-4 alkyl,
C1-4 alkoxy,
halogen,
-OCH₂CF₃,
15 -OCH₂CN,
-COOH,
-OH,
-COOR⁶, where R⁶ is C1-4alkyl,
-CONR⁷R⁸, where R⁷ and R⁸ are independently
20 hydrogen or C1-4alkyl,
-(CH₂)₁₋₄OH,
-CH₂NHC(O)CH₃,
-CH₂NHC(O)CF₃,
-CH₂NHSO₂CH₃,
25 -SO₂NH₂,
-(CH₂)₁₋₄SO₂NR⁷R⁸,
-(CH₂)₁₋₄SO₂R⁶,
a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
heterocyclic ring which can be saturated or unsaturated, and
30 which contains from one to four heteroatoms selected from the
group consisting of N, O and S,
-ZCH₂CO₂H,
-ZCH₂CO₂CH₃,
-ZCH₂R¹⁴,

- 6 -

-ZCH₂CO₂(CH₂)₁₋₃CH₃,
-Z(CHR⁹)₁₋₃C(O)NR¹⁰R¹¹,

wherein

R⁹ is H or C₁₋₄ alkyl,

5 R¹⁰ and R¹¹ are independently

hydrogen,

C₃₋₇ cycloalkyl,

aryl,

heteroaryl,

10 heterocycloalkyl,

-(CH₂)₁₋₂NCH₂CH₃,

C₁₋₄ alkyl unsubstituted or substituted with one or more
of:

hydroxy,

15 COOH,

amino,

aryl,

heteroaryl, or

heterocycloalkyl, or

20 R¹⁰ and R¹¹ are joined to form a four to seven
membered cycloalkyl ring unsubstituted or
substituted with hydroxy, amino or aryl,

wherein Z is O, S or CH₂;

25

R⁵ is

hydrogen,

halogen,

C₁₋₄ alkyl,

30 C₁₋₄ alkoxy,

CF₃,

CN, or

CO₂NH₂; and

- 7 -

R¹² is

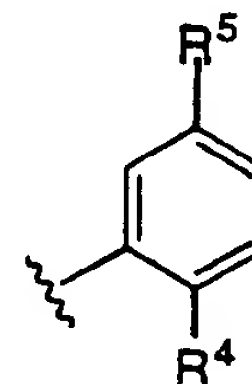
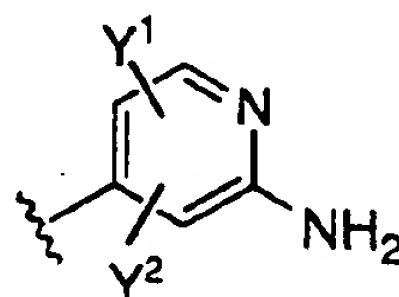
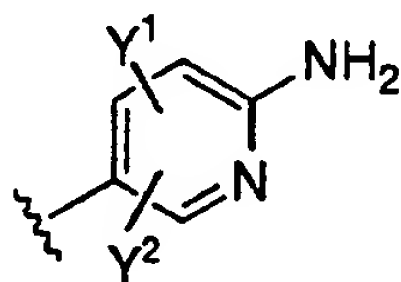
- hydrogen,
 phenyl, unsubstituted or substituted with one or more of C₁-4
 alkyl, C₁-4 alkoxy, halogen, hydroxy, COOH, CONH₂,
 5 naphthyl,
 biphenyl,
 a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
 heterocyclic ring which can be saturated or unsaturated, and
 which contains from one to four heteroatoms selected from the
 10 group consisting of N, O and S,
 C₁-4 alkyl, unsubstituted or substituted with one or more of
 hydroxy,
 COOH,
 amino,
 15 aryl,
 heteroaryl, or
 heterocycloalkyl,
 CF₃
 C₃-7 cycloalkyl,
 20 C₇-12 bicyclic alkyl, or
 C₁₀-16 tricyclic alkyl;

and pharmaceutically acceptable salts thereof.

- 25 In one class of compounds and pharmaceutically acceptable
 salts thereof, R³ is C₁-4 alkyl.

In a subclass of this class of compounds and
 pharmaceutically acceptable salts thereof,

A is chosen from one of the following radicals:



- 8 -

wherein Y^1 and Y^2 are independently hydrogen or C_{1-4} alkyl;

R^4 is

5 hydrogen,
 halogen,
 $-OCH_2CN$,
 $-OH$,
 $-ZCH_2CO_2H$, or
 $-Z(CHR^9)_{1-3}C(O)NR^{10}R^{11}$,

10

 wherein

R^9 is H or C_{1-4} alkyl, and

R^{10} and R^{11} are independently

 hydrogen,

C_{3-7} cycloalkyl,

15

$-(CH_2)_{1-2}NCH_2CH_3$, or

C_{1-4} alkyl,

 wherein Z is O, S or CH_2 ;

20 R^5 is

 hydrogen,
 halogen, or
 CF_3 .

25

 In a group of this subclass of compounds and
 pharmaceutically acceptable salts thereof, W is H or R^1 .

 In a subgroup of this group of compounds and
 pharmaceutically acceptable salts thereof, R^1 is

30

R^2 ,

$R^2(CH_2)_mC(R^{12})_2$, where m is 0-3, and each R^{12} can be the same
 or different,

$R^2C(R^{12})_2(CH_2)_m$, wherein m is 0-3, and each R^{12} can be the
 same or different, wherein $(R^{12})_2$ can also form a ring with
 C represented by C_{3-7} cycloalkyl,

- 9 -

(R²)₂CH(CH₂)_r, where r is 0-4 and each R² can be the same or different, and wherein (R²)₂ can also form a ring with CH represented by C₃₋₇ cycloalkyl, C₇₋₁₂ bicyclic alkyl, C₁₀₋₁₆ tricyclic alkyl, or a 5- to 7- membered mono- or bicyclic heterocyclic ring which can be saturated or unsaturated, and which contains from one to three heteroatoms selected from the group consisting of N, O and S, or

R²O(CH₂)_p, wherein p is 1-4;

R² and R¹⁴ are independently

10 phenyl, unsubstituted or substituted with one or more of C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxy, or SO₂NH₂,
a 5- to 7- membered mono- or a 9- to 10-membered bicyclic heterocyclic ring or non-heterocyclic ring which can be saturated or unsaturated, wherein the heterocyclic ring contains from one to
15 four heteroatoms selected from the group consisting of N, O and S, and wherein the heterocyclic or non-heterocyclic ring is unsubstituted or substituted with halogen or hydroxy,
C₁₋₇ alkyl, unsubstituted or substituted with one or more of
hydroxy,
20 COOH,
C₃₋₇ cycloalkyl,
CF₃,
N(CH₃)₂,
-C₁₋₃alkylaryl,
25 heteroaryl, or
heterocycloalkyl,
CF₃, or
C₃₋₇ cycloalkyl, unsubstituted or substituted with aryl; and

30 R¹² is

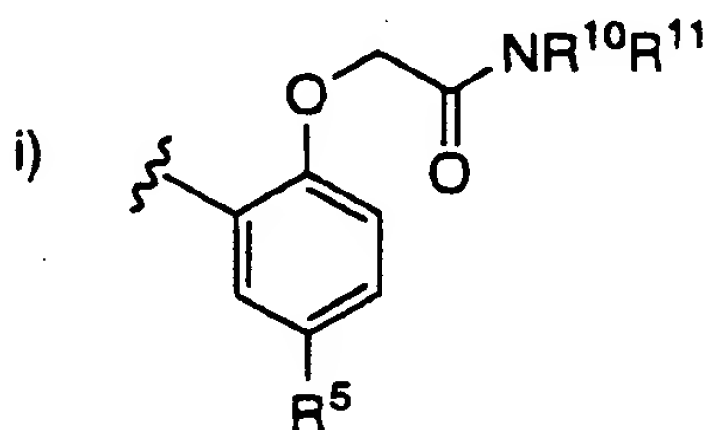
hydrogen,
C₁₋₄ alkyl, unsubstituted or substituted with one or more of
hydroxy,
COOH,

- 10 -

amino,
aryl,
heteroaryl, or
heterocycloalkyl.

5

In a family of this subgroup of compounds and
pharmaceutically acceptable salts thereof,
A is



10

wherein

R⁵ is H, fluoro, chloro, and

R¹⁰ and R¹¹ are independently selected from

15

H,

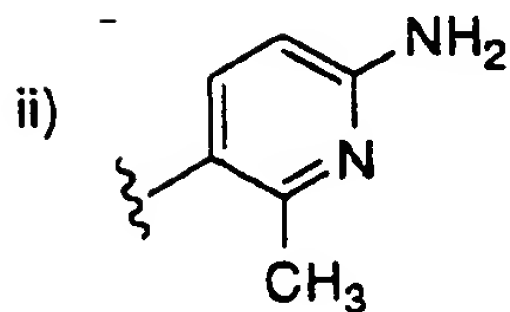
C₂H₅,

C₃H₅,

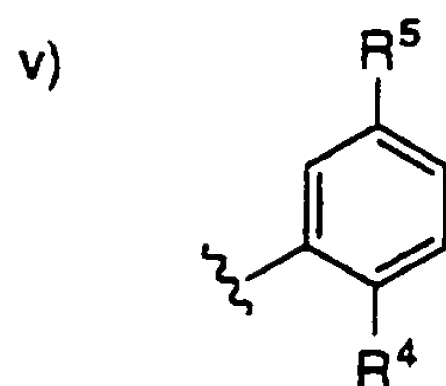
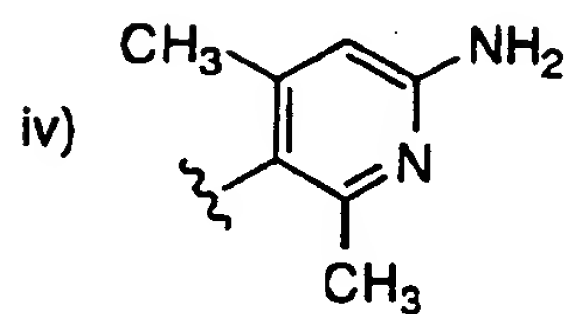
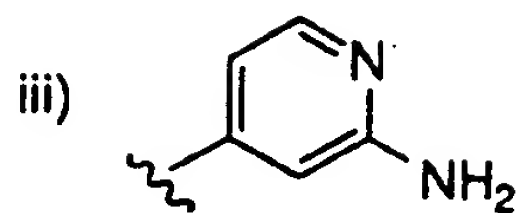
(CH₂)₂N(CH₃)₂,

C₃ cycloalkyl,

20

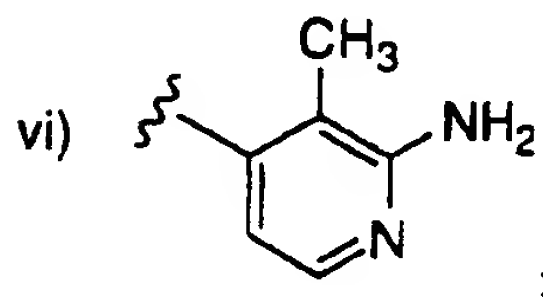


- 11 -



5

wherein R^4 is OH, chloro, H, $-OCH_2CN$, fluoro, $-OCH_2COOH$,
and R^5 is chloro or CF_3 ,



10

R^3 is CH_3 , or CH_2CH_3 ;

X is H or chloro; and

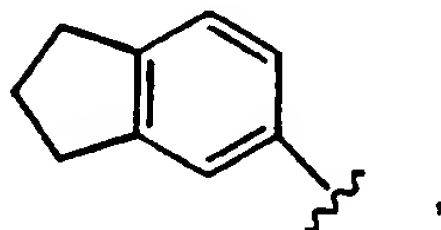
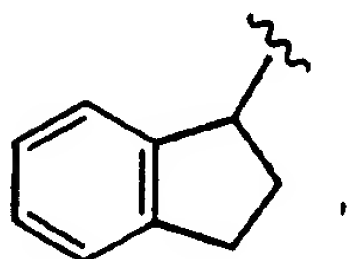
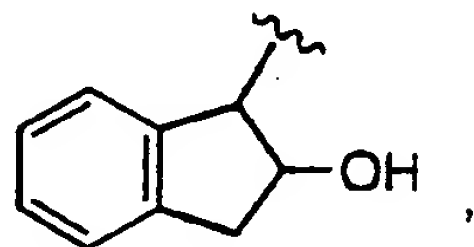
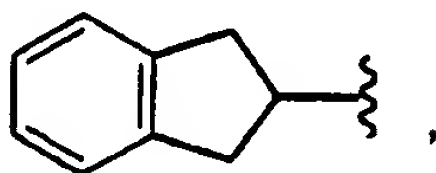
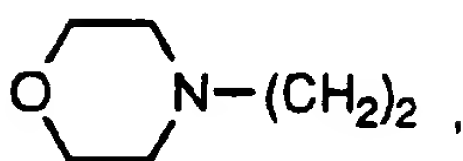
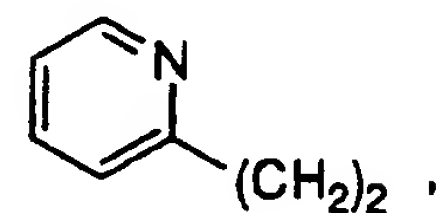
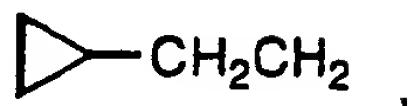
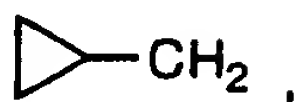
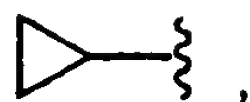
15 W is

$PhCH_2CH_2$,
 $(CH_3)_3C-$,

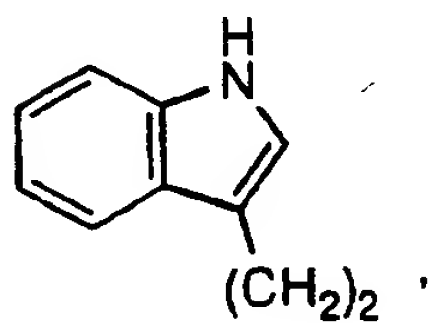
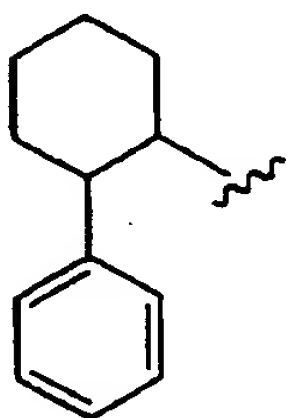
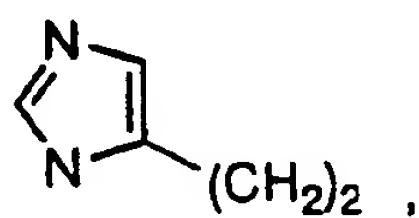
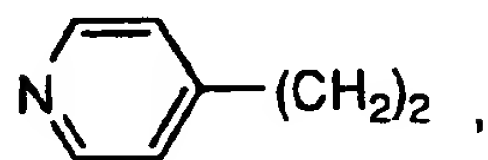
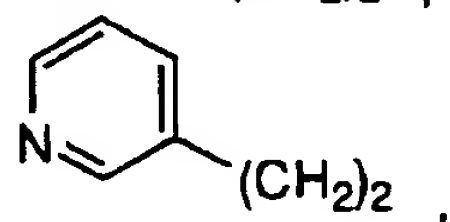
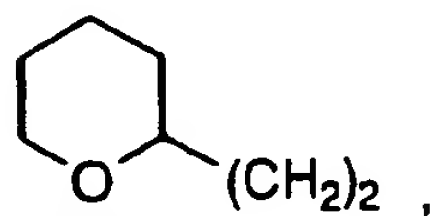
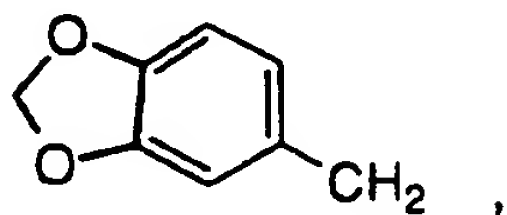
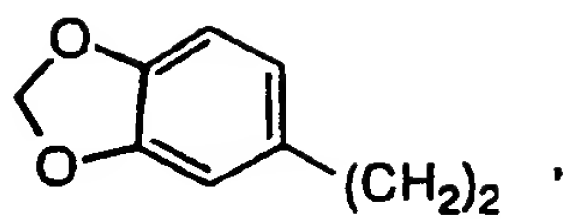
- 12 -

- 5 HOOCCH₂,
 CF₃CH₂,
 (CH₃)₂N(CH₂)₂,
 PhCH₂O(CH₂)₂,
 PhCH(CH₃),
 PhCH₂CH(COOH),
 CH₃(CH₂)₅,
 PhCH₂,
10 H,
 CH₃(CH₂)₄,
 CH₃CH₂CH(CH₃)CH₂,
 (Ph)₂CHCH₂,
 PhCH₂CH(CH₃),
 PhCH₂C(CH₃)₂,
15 PhCH(CH₃)CH₂,
 (CH₃)₂CH,
 PhCH(OH)CH₂,
 PhC(CH₃)CH₂,
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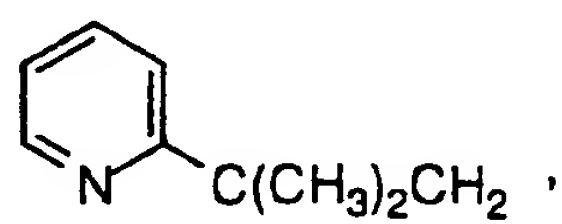
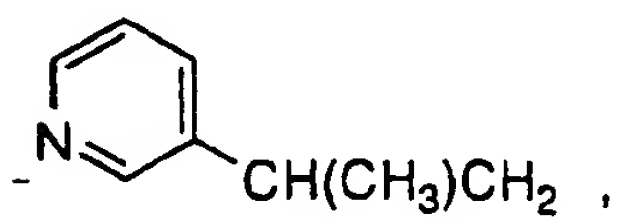
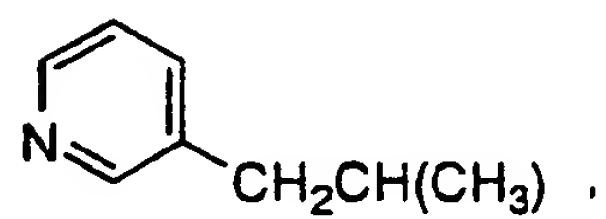
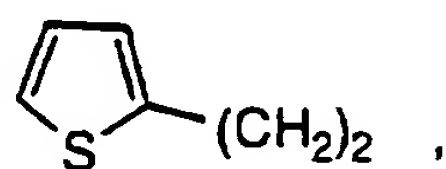
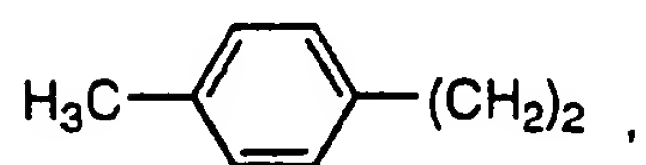
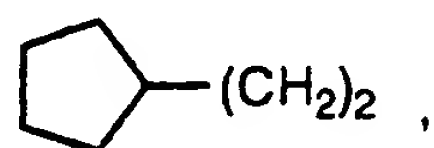
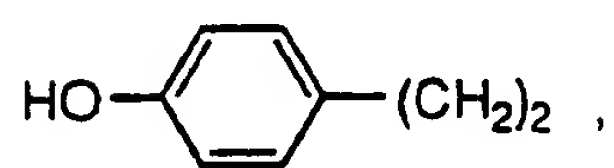
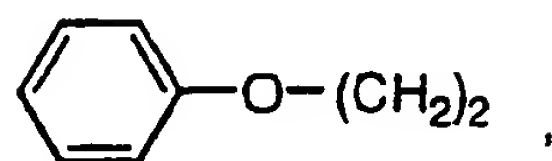
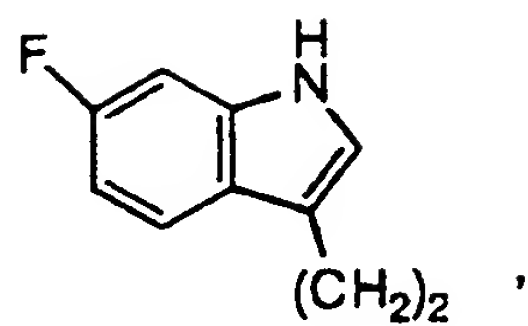
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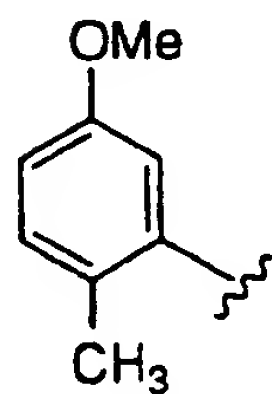
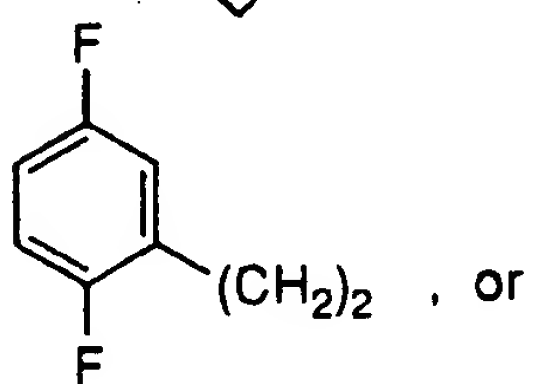
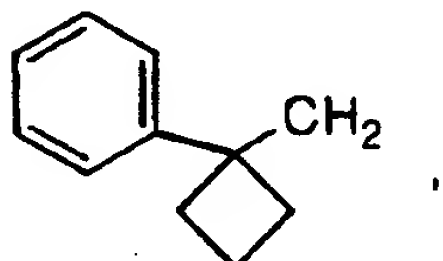
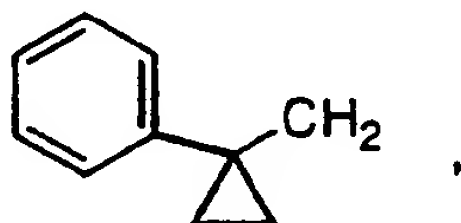
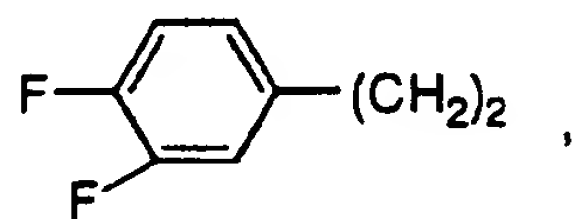
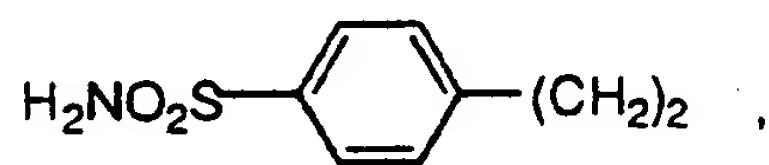
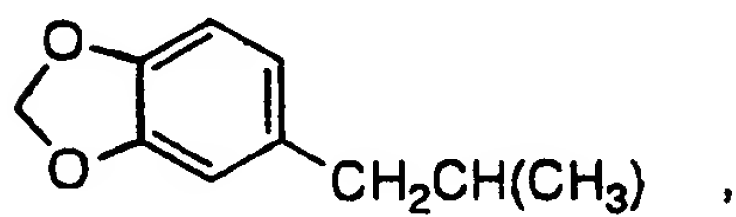
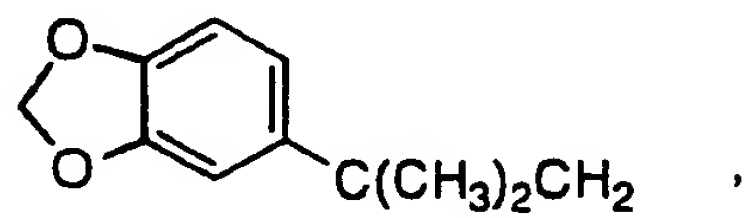
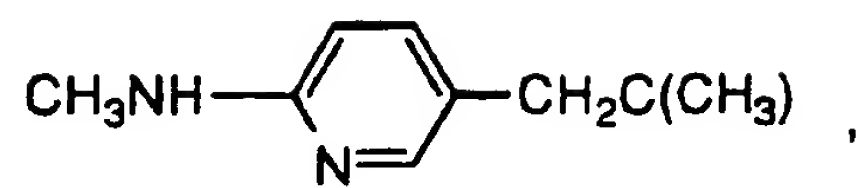
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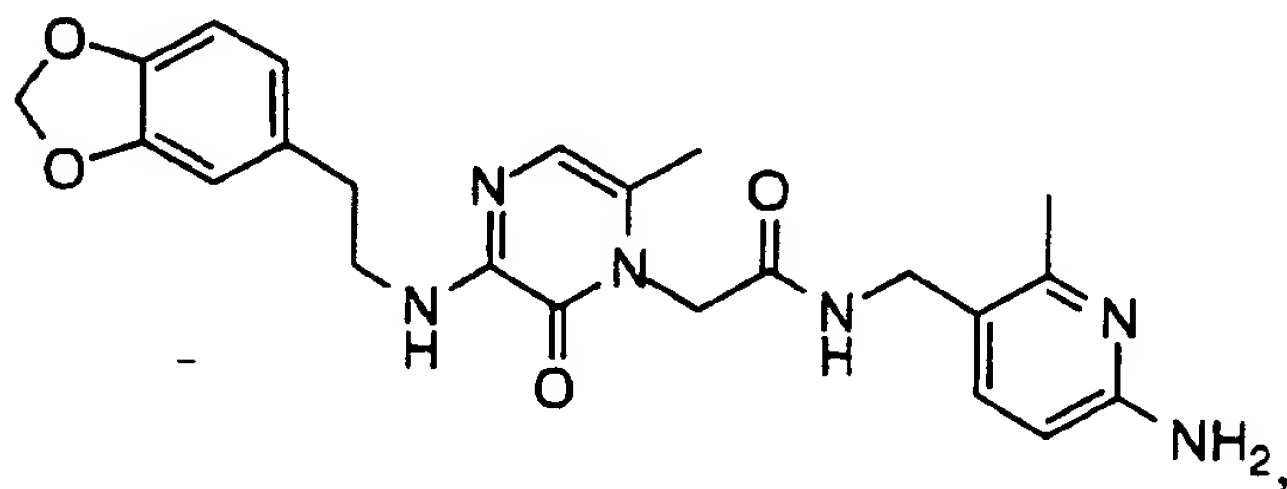
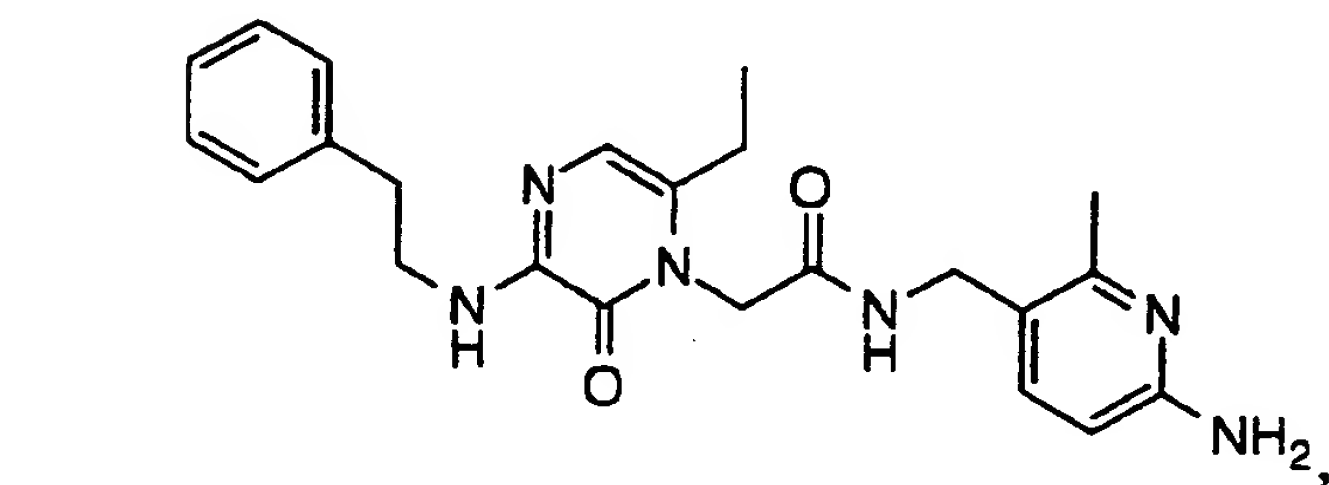
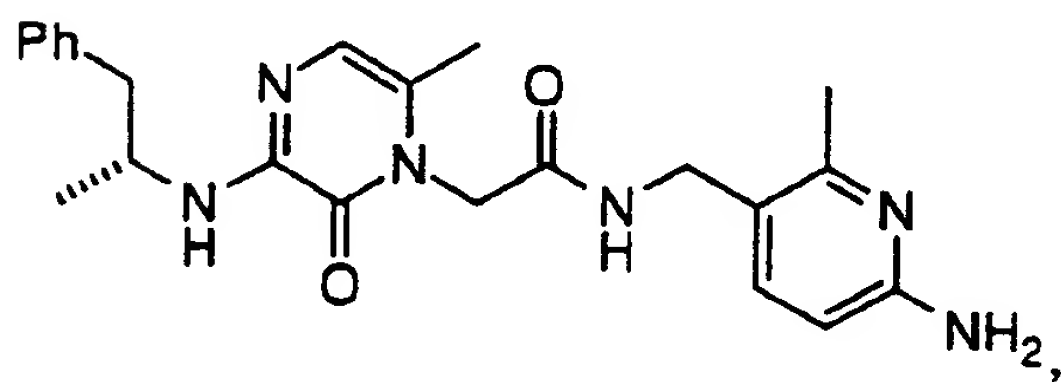
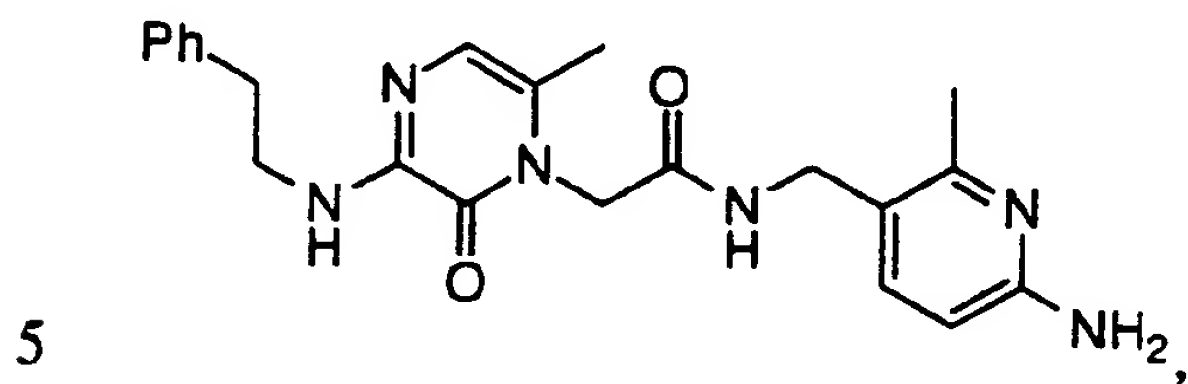


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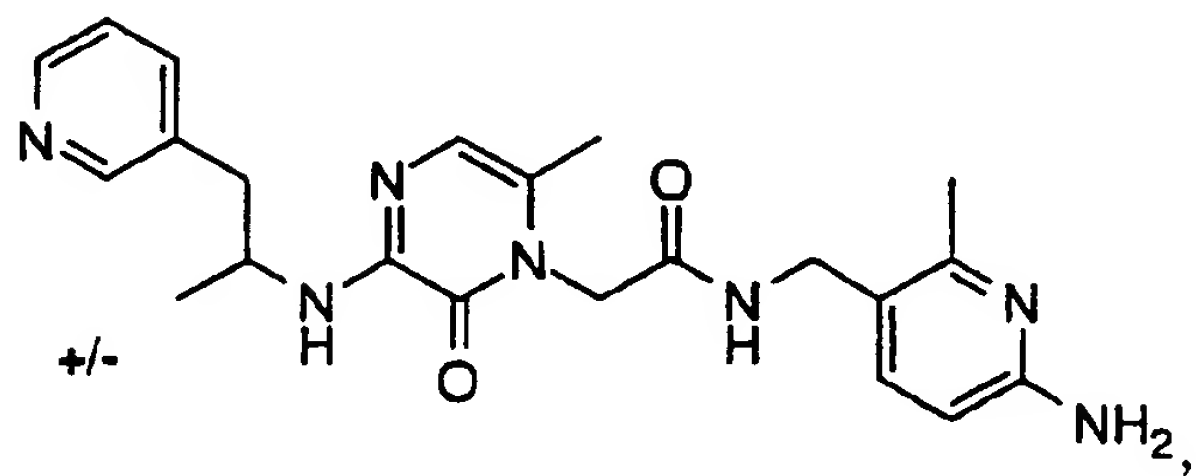
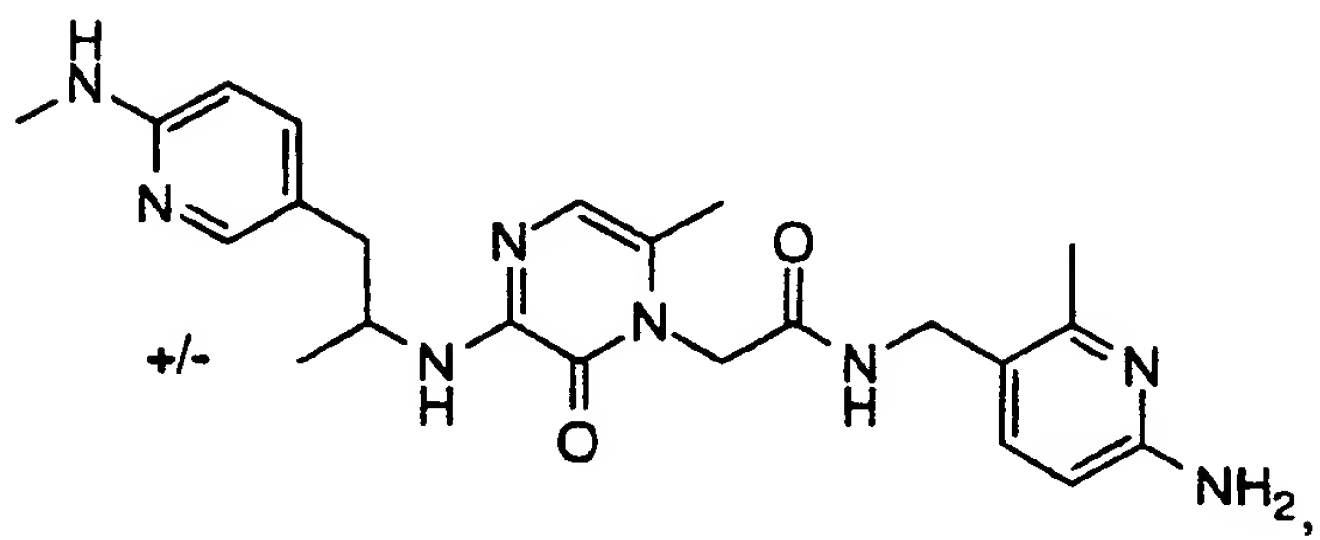
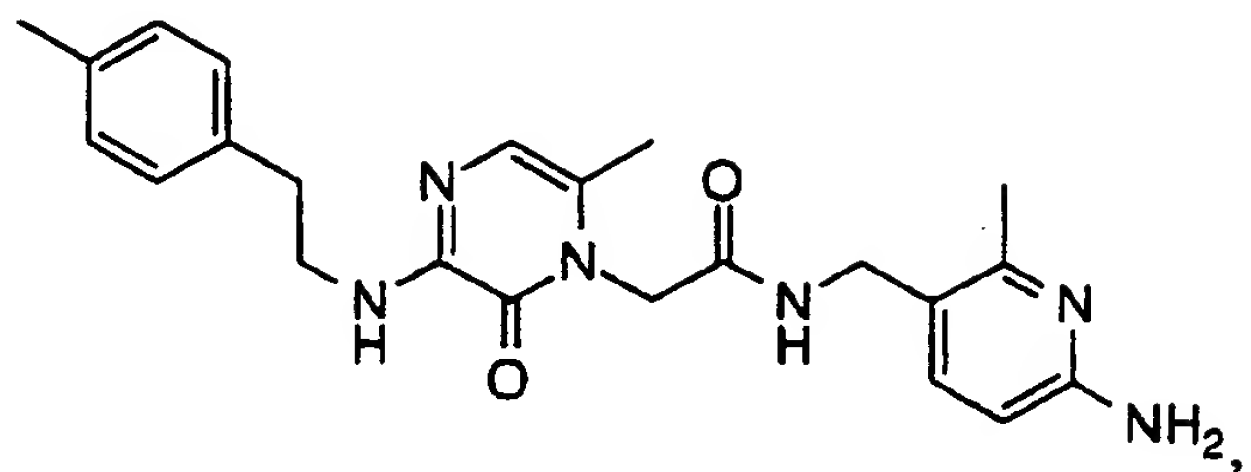


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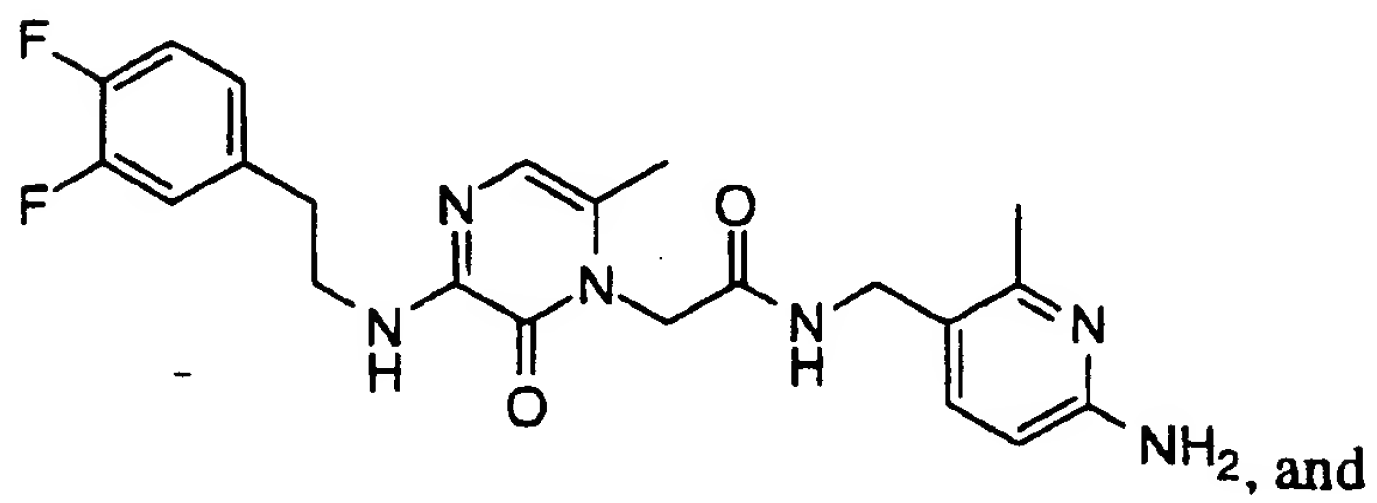
Examples of this family are listed in and following tables 1-4, and include (note that the methyl group is conventionally indicated as a single bond attached to a ring):



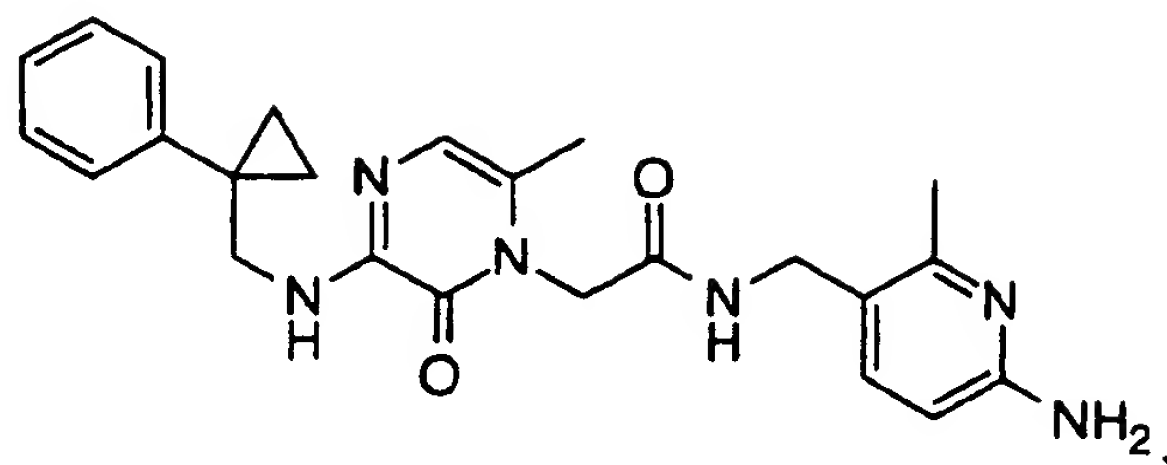
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- 19 -



One particular example is the compound 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone and pharmaceutically acceptable salts thereof. One particular salt of this compound is 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride. This salt can be prepared in one of two crystalline polymorphic forms, designated below as "Type A" and "Type B" (see example V).

The compounds of the present invention, may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. The compounds of the present invention may also have polymorphic crystalline forms, with all polymorphic crystalline forms being included in the present invention.

When any variable occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Some abbreviations that may appear in this application are as follows.

- 20 -

ABBREVIATIONSDesignation

BOC (Boc)

CBZ (Cbz)

TBS (TBDMS)

Protecting Group

t-butyloxycarbonyl

benzyloxycarbonyl(carbobenzoxy)

t-butyl-dimethylsilyl

Activating Group

HBT(HOBT or HOBt)

1-hydroxybenzotriazole hydrate

Designation

BOP reagent

Coupling Reagentbenzotriazol-1-yloxytris-
(dimethylamino)phosphonium
hexafluorophosphate

BOP-Cl

bis(2-oxo-3-oxazolidinyl)phosphinic
chloride

EDC

1-ethyl-3-(3-dimethylaminopropyl)
carbodiimide hydrochlorideOther(BOC)₂O (BOC₂O)

di-t-butyl dicarbonate

n-Bu₄N⁺F⁻

tetrabutyl ammonium fluoride

nBuLi (n-Buli)

n-butyllithium

DMF

dimethylformamide

Et₃N (TEA)

triethylamine

EtOAc

ethyl acetate

TFA

trifluoroacetic acid

DMAP

dimethylaminopyridine

DME

dimethoxyethane

NMM

N-methylmorpholine

DPPA

diphenylphosphoryl azide

THF

tetrahydrofuran

DIPEA

diisopropylethylamine

- 21 -

	<u>Amino Acid</u>
Ile	Isoleucine
Phe	Phenylalanine
Pro	Proline
Ala	Alanine
Val	Valine

As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl); "alkoxy" represents a linear or branched alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "Halo", as used herein, means fluoro, chloro, bromo and iodo; and "counterion" is used to represent a small, single negatively-charged species, such as chloride, bromide, hydroxide, acetate, trifluoroacetate, perchlorate, nitrate, benzoate, maleate, sulfate, tartrate, hemitartrate, benzene sulfonate, and the like.

The term "C3-7cycloalkyl" is intended to include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and the like.

The term "C7-12 bicyclic alkyl" is intended to include bicyclo[2.2.1]heptyl (norbornyl), bicyclo[2.2.2]octyl, 1,1,3-trimethyl-bicyclo[2.2.1]heptyl (bornyl), and the like.

The term "aryl" as used herein except where noted, represents a stable 6- to 10-membered mono- or bicyclic ring system such as phenyl, or naphthyl. The aryl ring can be unsubstituted or substituted with one or more of C₁₋₄ lower alkyl; hydroxy; alkoxy; halogen; amino. The term "heteroaryl" refers to a 5- to 7- membered unsaturated ring containing 1 or 2 heteroatoms selected from O, N, or S.

The term "heterocycle" or "heterocyclic ring", as used herein except where noted, represents a stable 5- to 7-membered mono- or bicyclic or stable 7- to 10-membered bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group

- 22 -

consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring.

5 Especially useful are rings containing one oxygen or sulfur, one to four nitrogen atoms, or one oxygen or sulfur combined with one or two nitrogen atoms. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure.

10 Examples of such heterocyclic groups include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodiny, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, 15 isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, tetrazole, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Morpholino is the same as morpholinyl.

20 The pharmaceutically-acceptable salts of the compounds of Formula I (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts such as those derived from inorganic acids, e.g. hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, or the quaternary ammonium salts which 25 are formed, e.g., from inorganic or organic acids or bases. Examples of acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, 30 hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, tosylate, and

- 23 -

undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

Thrombin Inhibitors - Therapeutic Uses- Method of Using

Anticoagulant therapy is indicated for the treatment and prevention of a variety of thrombotic conditions, particularly coronary artery and cerebrovascular disease. Those experienced in this field are readily aware of the circumstances requiring anticoagulant therapy. The term "patient" used herein is taken to mean mammals such as primates, including humans, sheep, horses, cattle, pigs, dogs, cats, rats, and mice.

Thrombin inhibition is useful not only in the anticoagulant therapy of individuals having thrombotic conditions, but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, the thrombin inhibitors can be added to or contacted with any medium containing or suspected of containing thrombin and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material selected from the group consisting of vascular grafts, stents, orthopedic prosthesis, cardiac prosthesis, and extracorporeal circulation systems.

Compounds of the invention are useful for treating or preventing venous thromboembolism (e.g. obstruction or occlusion of a vein by a detached thrombus; obstruction or occlusion of a lung artery by a detached thrombus), cardiogenic thromboembolism (e.g. obstruction or occlusion of the heart by a detached thrombus), arterial thrombosis (e.g. formation of a thrombus within an artery that may cause infarction of

- 24 -

tissue supplied by the artery), atherosclerosis (e.g. arteriosclerosis characterized by irregularly distributed lipid deposits) in mammals, and for lowering the propensity of devices that come into contact with blood to clot blood.

5 Examples of venous thromboembolism which may be treated or prevented with compounds of the invention include obstruction of a vein, obstruction of a lung artery (pulmonary embolism), deep vein thrombosis, thrombosis associated with cancer and cancer chemotherapy, thrombosis inherited with thrombophilic diseases such as Protein C
10 deficiency, Protein S deficiency, antithrombin III deficiency, and Factor V Leiden, and thrombosis resulting from acquired thrombophilic disorders such as systemic lupus erythematosus (inflammatory connective tissue disease). Also with regard to venous thromboembolism, compounds of the invention are useful for maintaining patency of
15 indwelling catheters.

 Examples of cardiogenic thromboembolism which may be treated or prevented with compounds of the invention include thromboembolic stroke (detached thrombus causing neurological affliction related to impaired cerebral blood supply), cardiogenic
20 thromboembolism associated with atrial fibrillation (rapid, irregular twitching of upper heart chamber muscular fibrils), cardiogenic thromboembolism associated with prosthetic heart valves such as mechanical heart valves, and cardiogenic thromboembolism associated with heart disease.

25 Examples of arterial thrombosis include unstable angina (severe constrictive pain in chest of coronary origin), myocardial infarction (heart muscle cell death resulting from insufficient blood supply), ischemic heart disease (local anemia due to obstruction (such as by arterial narrowing) of blood supply), reocclusion during or after
30 percutaneous transluminal coronary angioplasty, restenosis after percutaneous transluminal coronary angioplasty, occlusion of coronary artery bypass grafts, and occlusive cerebrovascular disease. Also with regard to arterial thrombosis, compounds of the invention are useful for maintaining patency in arteriovenous cannulas.

- 25 -

Examples of atherosclerosis include arteriosclerosis.

Examples of devices that come into contact with blood include vascular grafts, stents, orthopedic prosthesis, cardiac prosthesis, and extracorporeal circulation systems

5 The thrombin inhibitors of the invention can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups, and emulsions. Likewise, they may be administered in intravenous (bolus or infusion), intraperitoneal,
10 subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent. For treating ocular build up of fibrin, the compounds may be administered intraocularly or topically as well as orally or parenterally.

15 The thrombin inhibitors can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or
20 implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers manufactured by the Dow-Corning Corporation.

 The thrombin inhibitors can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large
25 unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

 The thrombin inhibitors may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound
30 molecules are coupled. The thrombin inhibitors may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues.

- 26 -

Furthermore, the thrombin inhibitors may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The dosage regimen utilizing the thrombin inhibitors is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of the thrombin inhibitors, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 30 mg/kg/day, preferably 0.025-7.5 mg/kg/day, more preferably 0.1-2.5 mg/kg/day, and most preferably 0.1-0.5 mg/kg/day (unless specified otherwise, amounts of active ingredients are on free base basis). For example, an 80 kg patient would receive between about 0.8 mg/day and 2.4 g/day, preferably 2-600 mg/day, more preferably 8-200 mg/day, and most preferably 8-40 mg/kg/day. A suitably prepared medicament for once a day administration would thus contain between 0.8 mg and 2.4 g, preferably between 2 mg and 600 mg, more preferably between 8 mg and 200 mg, and most preferably 8 mg and 40 mg, e.g., 8 mg, 10 mg, 20 mg and 40 mg. Advantageously, the thrombin inhibitors may be administered in divided doses of two, three, or four times daily. For administration twice a day, a suitably prepared medicament would contain between 0.4 mg and 4 g, preferably between 1 mg and 300 mg, more preferably between 4 mg and 100 mg, and most preferably 4 mg and 20 mg, e.g., 4 mg, 5 mg, 10 mg and 20 mg.

Intravenously, the patient would receive the active ingredient in quantities sufficient to deliver between 0.025-7.5 mg/kg/day, preferably 0.1-2.5 mg/kg/day, and more preferably 0.1-0.5 mg/kg/day.

- 27 -

Such quantities may be administered in a number of suitable ways, e.g. large volumes of low concentrations of active ingredient during one extended period of time or several times a day, low volumes of high concentrations of active ingredient during a short period of time, e.g. once a day. Typically, a conventional intravenous formulation may be prepared which contains a concentration of active ingredient of between about 0.01-1.0 mg/ml, e.g. 0.1 mg/ml, 0.3 mg/ml, and 0.6 mg/ml, and administered in amounts per day of between 0.01 ml/kg patient weight and 10.0 ml/kg patient weight, e.g. 0.1 ml/kg, 0.2 ml/kg, 0.5 ml/kg. In one example, an 80 kg patient, receiving 8 ml twice a day of an intravenous formulation having a concentration of active ingredient of 0.5 mg/ml, receives 8 mg of active ingredient per day. Glucuronic acid, L-lactic acid, acetic acid, citric acid or any pharmaceutically acceptable acid/conjugate base with reasonable buffering capacity in the pH range acceptable for intravenous administration may be used as buffers. Consideration should be given to the solubility of the drug in choosing an The choice of appropriate buffer and pH of a formulation, depending on solubility of the drug to be administered, is readily made by a person having ordinary skill in the art.

The compounds can also be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regime.

The thrombin inhibitors are typically administered as active ingredients in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixers, syrups and the like, and consistent with convention pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch,

- 28 -

sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch methyl cellulose, agar, bentonite, xanthan gum and the like.

Typical tablet cores suitable for administration of thrombin inhibitors are comprised of, but not limited to, the following amounts of standard ingredients:

Suggested Ranges of Composition for Excipients
in Uncoated Tablet Cores

Excipient	General Range (%)	Preferred Range (%)	Most Preferred Range (%)
mannitol	10-90	25-75	30-60
microcrystalline cellulose	10-90	25-75	30-60
magnesium stearate	0.1-5.0	0.1-2.5	0.5-1.5

Mannitol, microcrystalline cellulose and magnesium stearate may be substituted with alternative pharmaceutically acceptable excipients.

The thrombin inhibitors can also be co-administered with suitable anti-platelet agents, including, but not limited to, fibrinogen receptor antagonists (e.g. to treat or prevent unstable angina or to prevent

- 29 -

reocclusion after angioplasty and restenosis), anticoagulants such as aspirin, thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various vascular pathologies, or lipid lowering agents including
5 antihypercholesterolemics (e.g. HMG CoA reductase inhibitors such as lovastatin, HMG CoA synthase inhibitors, etc.) to treat or prevent atherosclerosis. For example, patients suffering from coronary artery disease, and patients subjected to angioplasty procedures, would benefit from coadministration of fibrinogen receptor antagonists and thrombin
10 inhibitors. Also, thrombin inhibitors enhance the efficiency of tissue plasminogen activator-mediated thrombolytic reperfusion. Thrombin inhibitors may be administered first following thrombus formation, and tissue plasminogen activator or other plasminogen activator is administered thereafter.

15 Typical doses of thrombin inhibitors of the invention in combination with other suitable anti-platelet agents, anticoagulation agents, or thrombolytic agents may be the same as those doses of thrombin inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, or thrombolytic agents, or
20 may be substantially less than those doses of thrombin inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, or thrombolytic agents, depending on a patient's therapeutic needs.

25 The following synthetic methods can be used to prepare the compounds of the present invention:

The following examples are illustrative of the invention as contemplated by the inventors and should not be construed as being limits on the scope or spirit of the instant invention.

30 METHOD 1 (Exemplified by Example I)

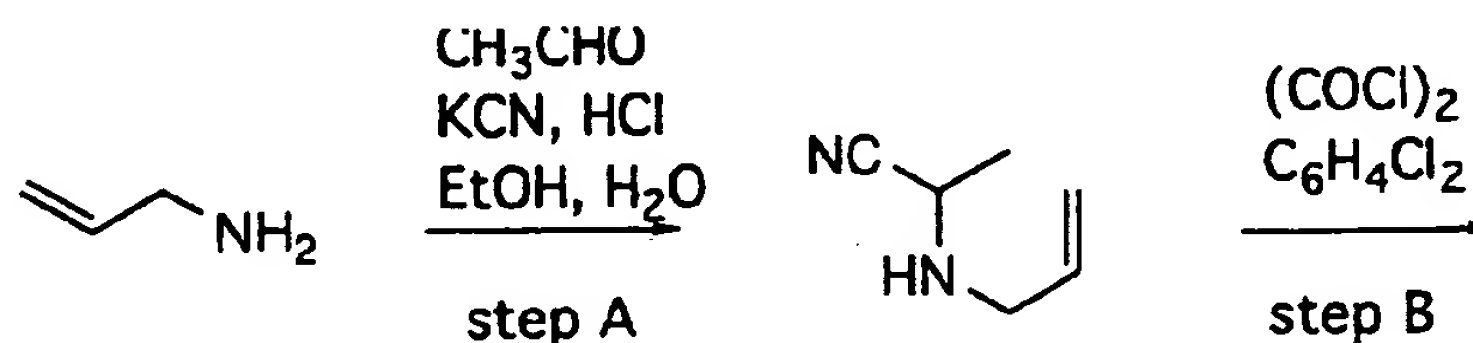
Starting allylamine is condensed with acetaldehyde and cyanide in Step A to afford the aminonitrile. This is reacted in Step B with oxalyl chloride according to the method of Hoormaert [J.

- 30 -

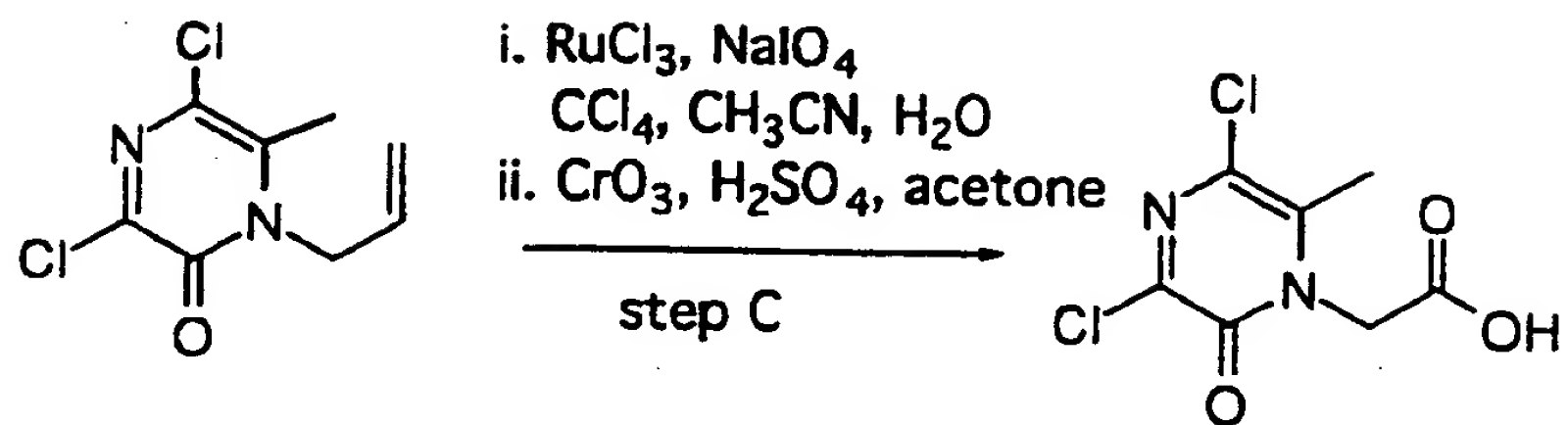
Heterocyclic Chem., 20, 919, (1983)] to give the pyrazinone. The olefin is oxidatively cleaved with ruthenium tetroxide and the resulting aldehyde is converted to the acid by an oxidising agent such as chromic acid in Step C. The 3-chloro group is then displaced by an ammonia equivalent, in this case *p*-methoxybenzylamine in Step D. The remaining chlorine is removed by reduction with Raney nickel in Step E and in Step F the *p*-methoxybenzyl group is removed by treatment with a strong acid such as TFA. Finally, in Step G, the acid is coupled to the appropriate amine, in this case ethyl-2-aminomethyl-4-chlorophenoxyacetamide to give the final product (a method for the preparation of this amine is given below).

METHOD 1 (Exemplified By Example I)

15

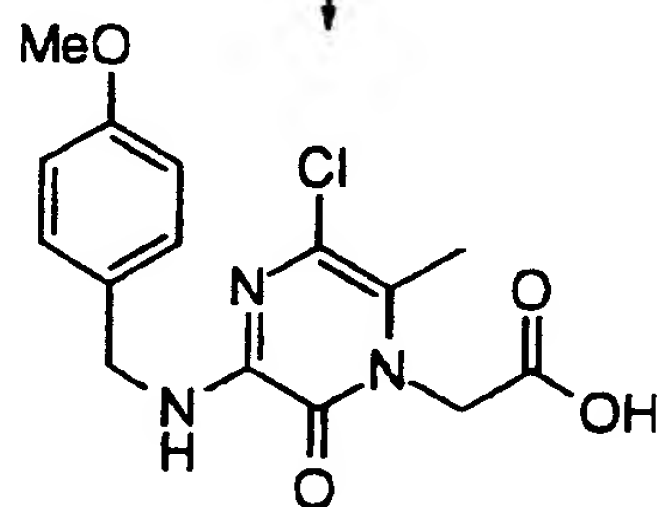


- 31 -



4-MeOPhCH₂NH₂,
Et₃N,
dioxane

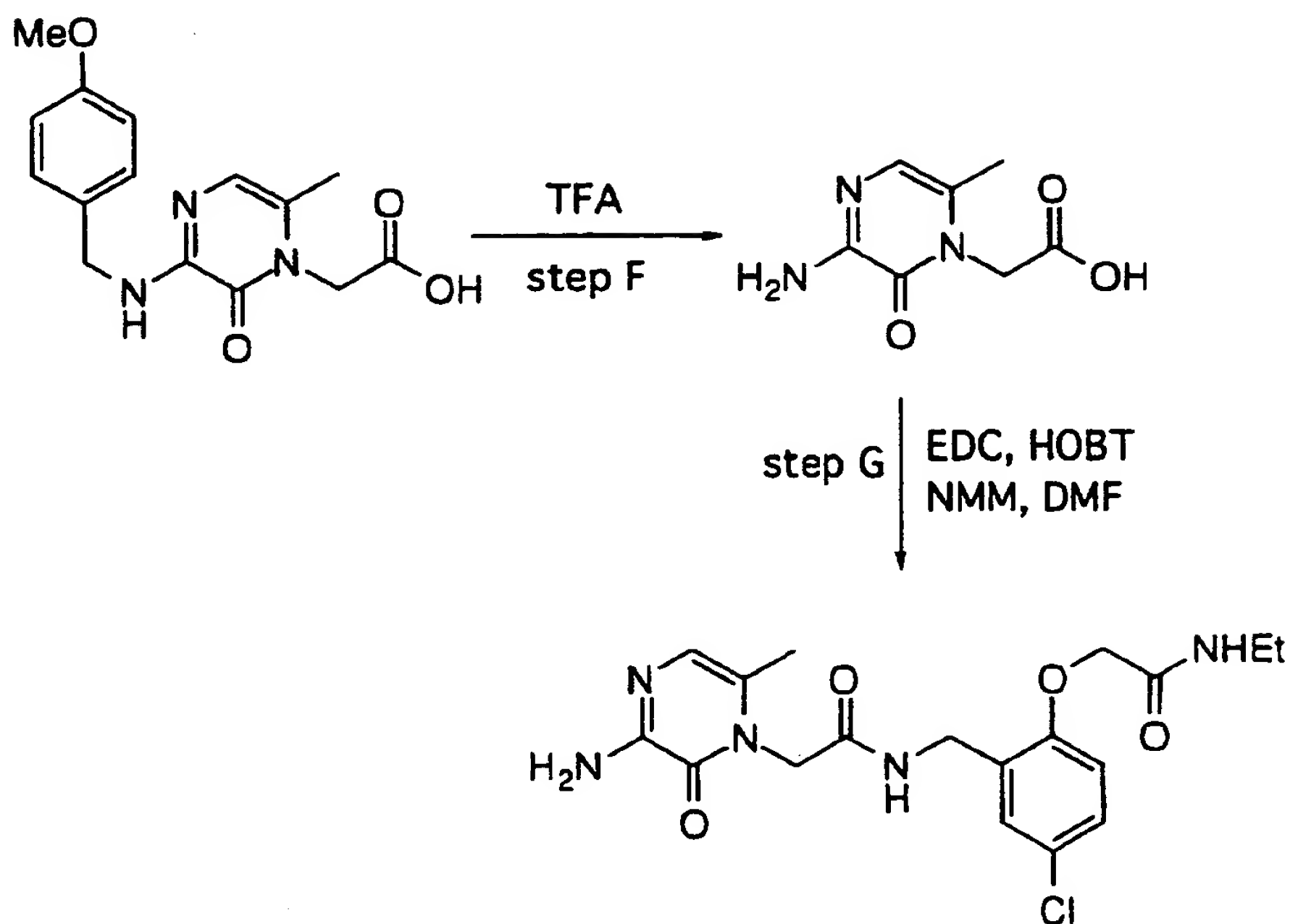
step D



step E

RaNi, NaOH

- 32 -



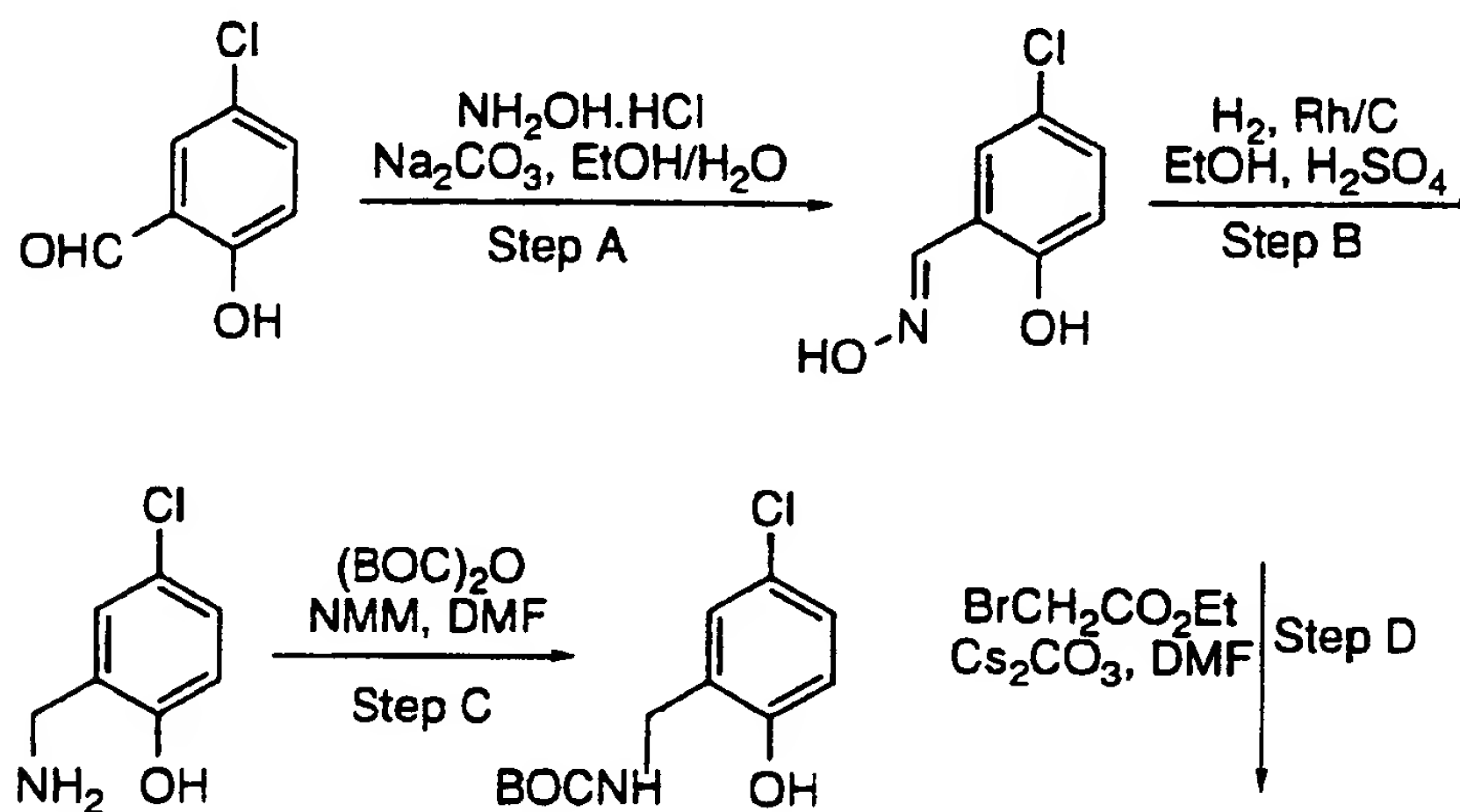
Amide couplings, e.g., Step G, to form the compounds of this invention can be performed by the carbodiimide method with reagents such as dicyclohexylcarbodiimide, or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide. Other methods of forming the amide or peptide bond include, but are not limited to the synthetic routes via an acid chloride, azide, mixed anhydride or activated ester. Typically, solution phase amide couplings are performed, but solid-phase synthesis by classical Merrifield techniques may be employed instead. The addition and removal of one or more protecting groups is also typical practice.

Modifications of the method will allow different W, R^3 , X and A groups contemplated by the scope of the broad claim below to be present by the use of an appropriate reagent or appropriately substituted starting material in the indicated synthetic step. For example the starting aldehyde in Step A can have as its side chain, ethyl, isopropyl, cyclopropyl, trifluoromethyl, and the like, to achieve the different operable values of R^3 . Likewise, different W groups can be present by

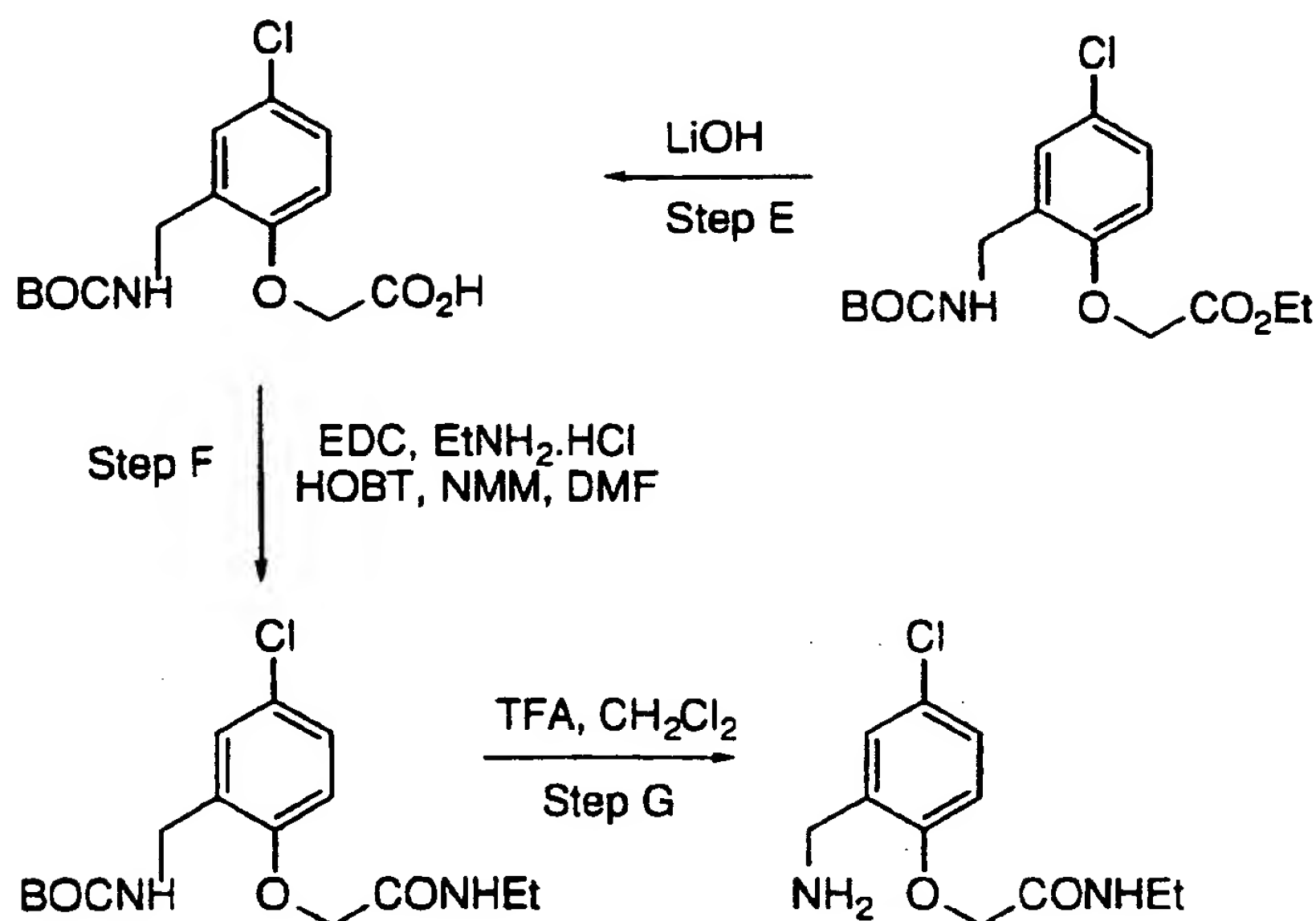
- 33 -

the use of an appropriate amine in Step D. Different X groups can be present by the omission of step E, and by the use of a reagent such as oxalyl bromide in step B. An appropriate choice of the amine in Step G will allow the different operable values of A to be achieved. Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

Method For Making Ethyl-2-Aminomethyl-4-Chlorophenoxyacetamide



- 34 -



Modifications of this method will allow different R⁴ and R⁵ groups contemplated by the scope of the broad claim below to be present by the use of an appropriate reagent or appropriately substituted starting material in the indicated synthetic step. For example, appropriate choice of the amine in Step F will allow different values of R¹⁰ and R¹¹ to be achieved. Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

10

Step A: 4-Chlorosalicaldehyde Oxime

A solution of hydroxylamine hydrochloride (16.7 g, 0.24 mol) and sodium carbonate (12.7 g, 0.12 mol) in water (120 ml) was added to a stirred solution of 4-chlorosalicaldehyde (25.0 g, 0.16 mol) in ethanol (160 ml) and the resulting solution was heated to reflux. After 1 h the reaction was cooled, water (320 ml) was added and the resulting crystalline precipitate was isolated by filtration. A second crop was similarly collected and the combined solids were dried to give the title compound:

15

- 35 -

¹H NMR (400 Mz, CDCl₃) δ 6.92 (d, J=8.8Hz, 1 H), 7.15 (d, J=2.6Hz, 1H), 7.23 (dd, J=2.6 and 8.8 Hz, 1H), 7.26 (s, 1H), 8.16 (s, 1H), 9.71 (s, 1H).

5 Step B: 2-Hydroxy-5-Chlorobenzylamine

A mixture of 4-chlorosalicylaldehyde oxime (10 g, 58.3 mmol) and 5% Rh/C (2.0 g) in ethanol (100 ml) containing concentrated sulfuric acid (10 ml) was shaken in a Parr apparatus under H₂ (60 psi) for 24 h. Water (100 ml) was added and the mixture was filtered through celite.

10 The filtrate was concentrated until the product had crystallized out of solution. The solid was collected by filtration and the filtrate was further concentrated, adding water to give a second crop which was combined with the first to give, after drying the title compound, the sulfate salt:
¹H NMR (400 Mz, CD₃OD) δ 4.07 (s, 2 H), 6.88 (d, J=8.6Hz, 1 H), 7.25
15 (dd, J=2.6 and 8.6Hz, 1H), 7.31 (d, J=2.6Hz, 1 H).

Step C: N-t-Butoxycarbonyl-2-Hydroxy-5-Chlorobenzylamine

A mixture of 2-hydroxy-5-chlorobenzylamine (1.22 g, 4.77 mmol assuming the bisulfate salt), (BOC)₂O (1.56 g, 7.16 mmol) and N-methylmorpholine (1.05 ml, 9.54 mmol) in DMF (10 ml) was stirred for 5
20 h at r.t. The reaction was partitioned between water and ethyl acetate and the organic layer was washed with 5% KHSO₄ solution (2 times), sodium hydrogen carbonate solution and brine, dried (Na₂SO₄) and evaporated *in vacuo* to a solid. The crude product was recrystallized from ethyl
25 acetate/hexanes (1:5, 12 ml) to give the title compound:
¹H NMR (400 Mz, CDCl₃) δ 1.44 (s, 9 H, t-Bu), 4.17 (d, J=6.8Hz, 2H, CH₂), 5.22 (br t, 1H, NH), 6.87 (d, J=8.6Hz, 1H, H-3), 7.03 (d, J = 2.6Hz, 1H, H-6), 7.15 (dd, J=2.6 and 8.6 Hz, 1H, H-4).

30 Step D: Ethyl-2-t-Butoxycarbonylaminomethyl-4-Chlorophen-
oxyacetate

A mixture of N-t-butoxycarbonyl-2-hydroxy-5-chlorobenzylamine (730 mg, 2.83 mmol), Cs₂CO₃ (923 mg, 2.83 mmol) and ethylbromoacetate (0.314 ml, 2.83 mmol) in DMF (5 ml) was stirred for 2

- 36 -

h. The crude reaction mixture was partitioned between ethyl acetate and water and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo* to an oil which was used for the next step.

5 Step E: 2-t-Butoxycarbonylaminomethyl-4-Chlorophenoxyacetic Acid

 The product from Step D was suspended in 1:1:1 methanol/THF/ water (9 ml) and lithium hydroxide hydrate (126 mg, 3.0 mmol) was added. After 16 h the volatiles were removed *in vacuo* and
10 the solution was diluted with water and was washed with ethyl acetate, adding sufficient brine to disperse the emulsion. The aqueous layer was acidified with 5% KHSO_4 solution and was extracted with methylene chloride which was then dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a solid:
15 ^1H NMR (400 Mz, CDCl_3) δ 1.44 (s, 9H, t-Bu), 4.35 (br s, 2H, NCH_2), 4.62 (s, 2H, OCH_2), 5.04 (br s, 1H, NH), 6.74 (d, $J=7.9\text{Hz}$, 1H, H-3), 7.20 (d, $J=2.6\text{Hz}$, 1H, H-6), 7.24 (d obscured, 1H, H-4).

20 Step F: Ethyl-2-t-Butoxycarbonylaminomethyl-4-Chlorophenoxyacetamide

 EDC Hydrochloride (249 mg, 1.3 mmol) was added to a stirred mixture of 2-t-butoxycarbonylaminomethyl-4-chlorophenoxyacetic acid (316 mg, 1.0 mmol), HOBT (176 mg, 1.3 mmol), ethylamine hydrochloride (106 mg, 1.3 mmol) and N-methylmorpholine
25 (0.396 ml, 3.6 mmol) in DMF (4 ml) and the mixture was stirred for 16 h. The reaction was partitioned between ethylacetate and 5% KHSO_4 solution and the organic layer was washed with 5% KHSO_4 solution, water, NaHCO_3 solution and brine, dried (Na_2SO_4) and evaporated *in vacuo* to a solid (333 mg) which was used for the next step.

30

Step G: Ethyl-2-Aminomethyl-4-Chlorophenoxyacetamide

 Ethyl-2-t-butoxycarbonylaminomethyl-4-chlorophenoxyacetamide from Step F was dissolved in 2:1 methylene chloride/TFA (3 ml) and after 15 min the solvent was evaporated *in*

- 37 -

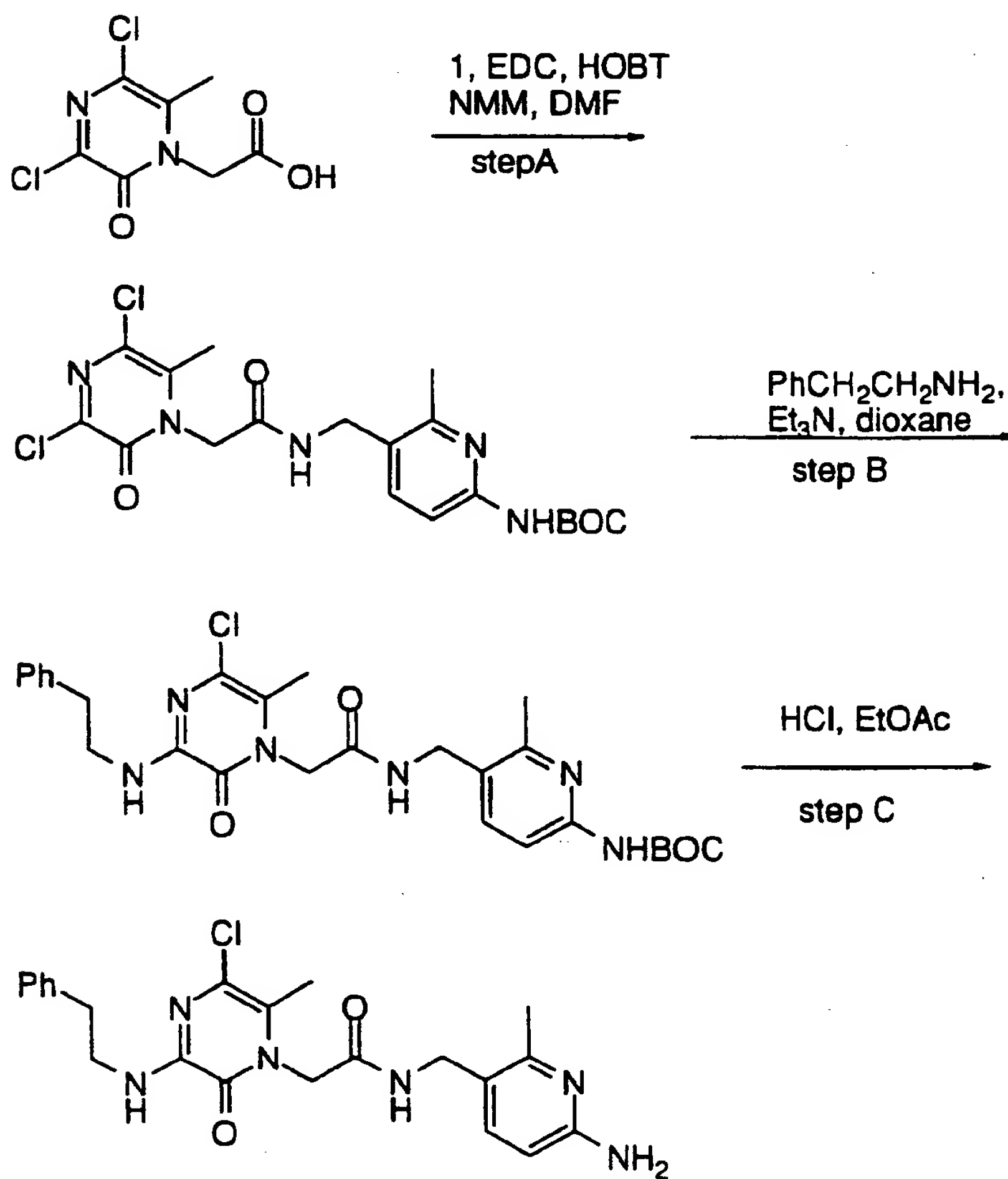
vacuo. The residue was dissolved in water and the solution was washed with methylene chloride (twice). The aqueous layer was then basified with saturated sodium carbonate solution and NaCl was added to saturation. The mixture was extracted with ethyl acetate, and the organic
5 layer was dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound as a crystalline solid:
¹H NMR (300 MHz, CDCl₃) δ 1.12 (t, J=7.3 Hz, 3H, Me), 1.54 (s, 9H, t-Bu), 3.31 (quintet, J=7.3 Hz, 2H, CH₂Me), 3.90 (s, 2H, NCH₂), 4.58 (s, 2H, OCH₂), 6.80 (d, J=8.3 Hz, 1H, H-3), 7.19-7.23 (m, 2H, H-4, H-6),
10 8.01 (br s, 1H, CONH).

METHOD 2 (Exemplified By Example III)

An alternative method for preparing compounds of the
15 present invention is exemplified by Example II.

The acid from METHOD I, Step C is coupled to the appropriate amine, in this case 2-t-butoxycarbonylamino-5-aminomethyl-6-methylpyridine (a method for the preparation of this amine is shown below) in Step A. The 3-chloro group is then displaced by the
20 appropriate amine, in this case phenethylamine in Step B and the BOC group is then removed in Step C to give the final product.

- 38 -

METHOD 2 (Exemplified By Example II)

5 Modifications of the method will allow different W, R³, X and A groups contemplated by the scope of the broad claim below to be present by the use of an appropriate reagent or appropriately substituted starting material in the indicated synthetic step. Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

- 39 -

Method For Making 2-t-Butoxycarbonylamino-5-Aminomethyl-6-Methylpyridine

Preparation of 2-Amino-5-cyano-6-methylpyridine

- 5 A mixture of 6-amino-3-bromo-2-methylpyridine (20.0 g, 0.107 mol)(Maybridge) and copper (I) cyanide 11.0 g, 0.123 mol) in DMF (25 ml) was heated to reflux for 4 h. The DMF was evaporated *in vacuo* and the residue was partitioned between ethyl acetate and 10% sodium cyanide solution. The organic layer was washed with 10%
10 sodium cyanide solution and brine, dried (Na₂SO₄) and evaporated *in vacuo* to a brown solid. This was dissolved in a minimum amount of ethyl acetate and the product was precipitated by adding hexanes. The mixture was filtered to give the title compound as a brown powder:
15 ¹H NMR (CDCl₃) δ 2.56 (s, 3 H), 4.97 (br s, 2 H), 6.33 (d, J = 8.6 Hz, 1 H), 7.54 (d, J = 8.6 Hz, 1 H).

Preparation of 2-t-Butoxycarbonylamino-5-cyano-6-methylpyridine

- A mixture of 2-amino-5-cyano-6-methylpyridine (10.0 g, 75.1 mmol), (BOC)₂O (16.39 g, 75.1 mmol), triethylamine (11.5 ml, 82.6
20 mmol) and DMAP (0.92 g, 7.5 mmol) in methylene chloride (200 ml) was stirred for 3 h. More triethylamine (4.22 ml) and (BOC₂)O (1.64 g) were added and after 16 h the reaction was diluted with ethyl acetate and was washed with 1 M AcOH (3 times), dried (Na₂SO₄) and evaporated
25 *in vacuo* to give dark brown solid. The crude product was purified by flash column chromatography (10% ethylacetate/hexanes) to give the title compound as a white solid:
¹H NMR (CDCl₃) δ 1.52 (s, 9 H), 2.62 (s, 3 H), 7.46 (br s, 1 H), 7.80 (d, J = 8.8 Hz, 1 H), 7.88 (d, J = 8.8 Hz, 1 H).

- 30 Preparation of 2-t-Butoxycarbonylamino-5-aminomethyl-6-methylpyridine

A mixture of 2-t-butoxycarbonylamino-5-cyano-6-methylpyridine (14.68 g, 62.9 mmol) and 10% Pd/C (1.5 g) in glacial acetic acid (150 ml) was shaken on a Parr apparatus at 60 psi for 88 h.

- 40 -

The reaction was filtered through celite and was evaporated *in vacuo*. The residue was dissolved in water and the solution was washed with methylene chloride (2 times), then was basified with sodium carbonate and extracted with ethyl acetate (2 times). The combined ethyl acetate
5 layers were dried (Na₂SO₄) and evaporated *in vacuo* to a solid. The crude product was recrystallized (ethyl acetate/hexanes) to give the title compound:

¹H NMR (CDCl₃) δ 1.50 (s, 9 H), 2.43 (s, 3 H), 3.81 (s, 2 H), 7.23 (br s, 1 H), 7.57 (d, J = 8.3 Hz, 1 H), 7.70 (d, J = 8.3 Hz, 1 H).

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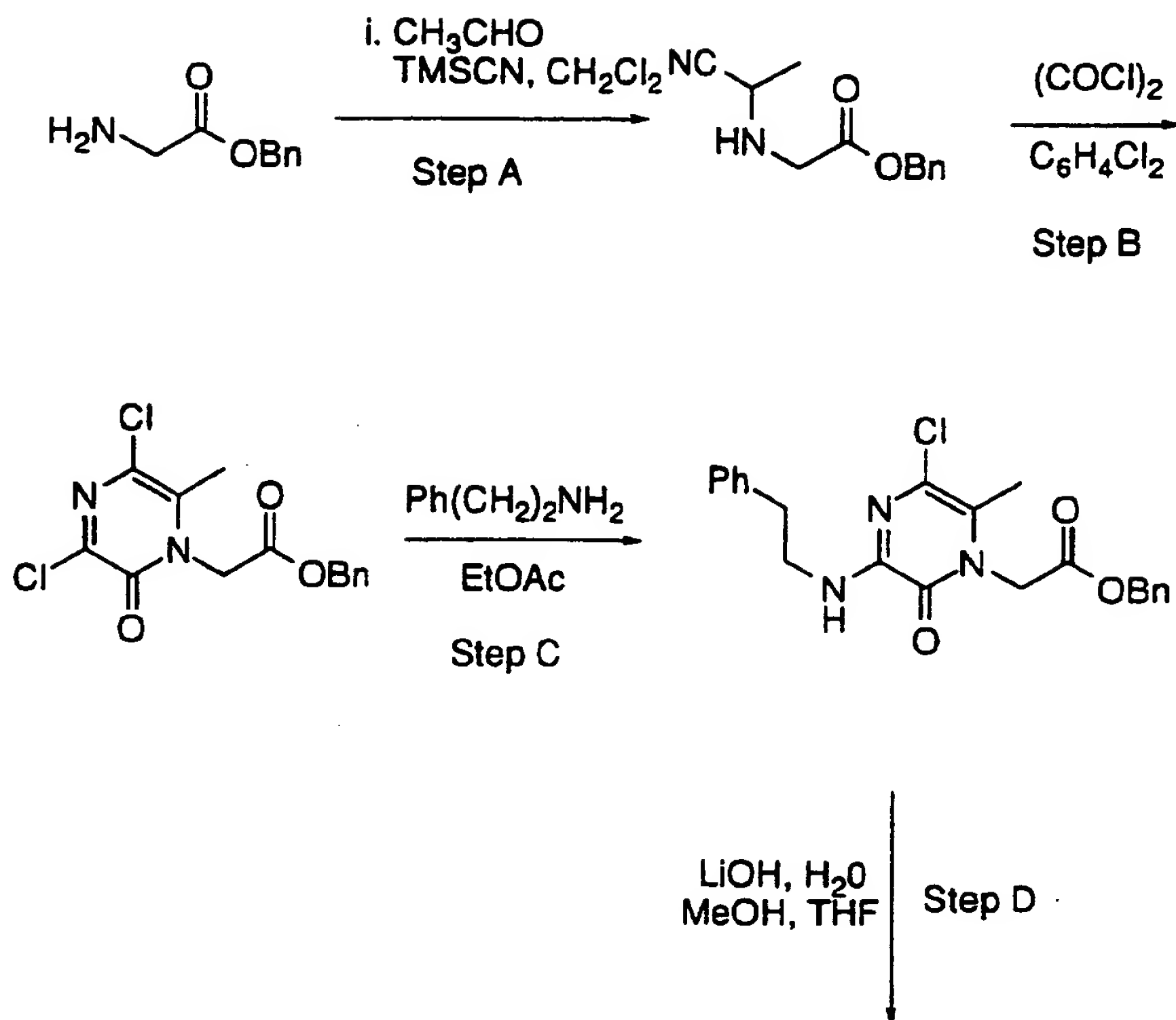
Modifications of this method will allow different Y¹ and Y² groups contemplated by the scope of the broad claim below to be present by the use of an appropriate reagent or appropriately substituted starting material in the indicated synthetic step. Obvious variations and
15 modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

METHOD 3 (Exemplified by Example V)

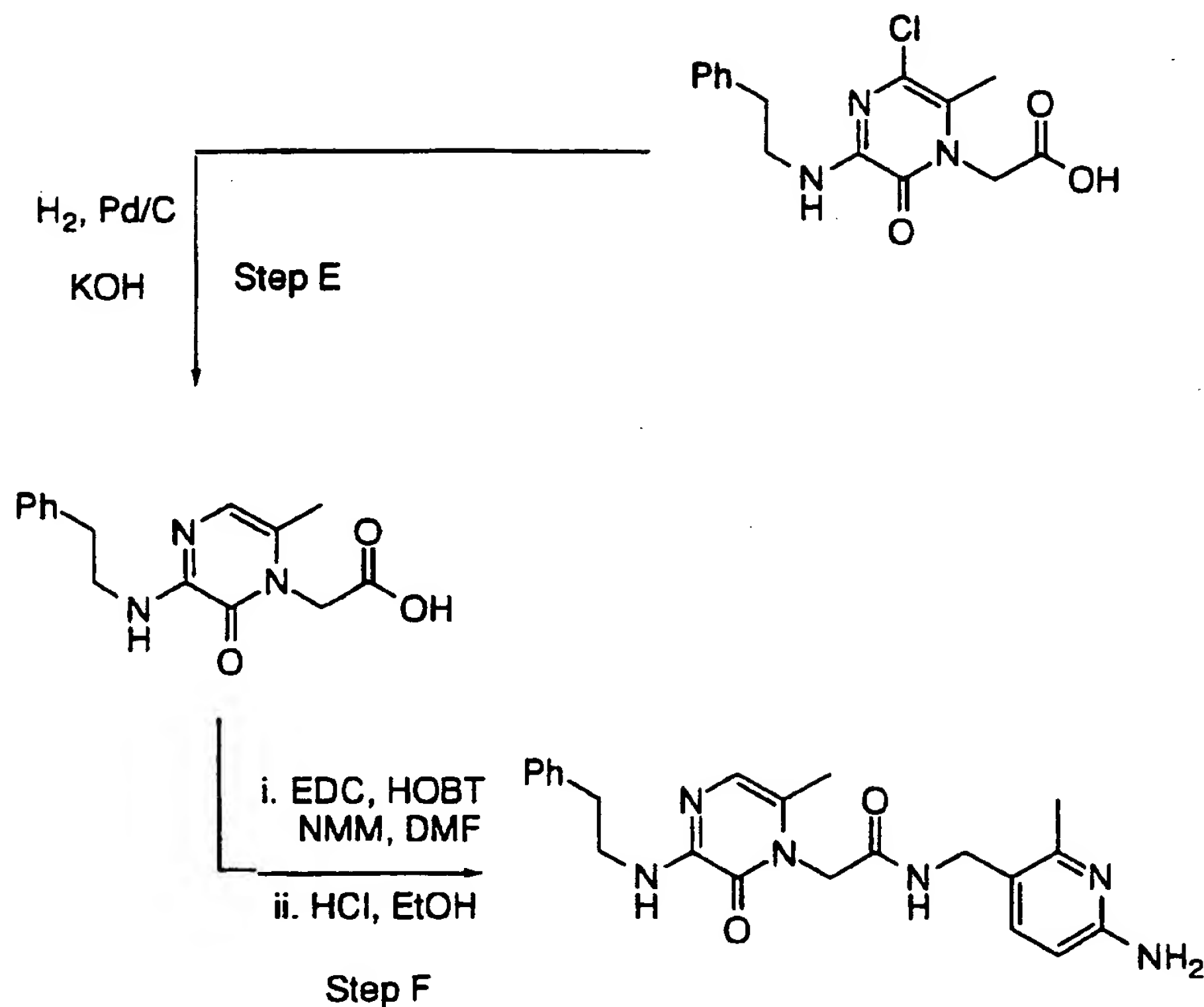
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An ester of glycine, in this case the benzyl ester, is condensed with acetaldehyde and cyanide in Step A to afford the aminonitrile. This is reacted in Step B with oxalyl chloride to give the pyrazinone. The 3-chloro group is then displaced by the appropriate amine, in this case phenethylamine, in Step C. The ester is hydrolysed in
25 Step D and the remaining chlorine is then removed by hydrogenolysis in Step E. The acid is then coupled in Step F with the appropriate amine, in this case 2-amino-5-aminomethyl-6-methylpyridine (a method for the preparation of this amine is shown below) to afford the final product.

- 41 -



- 42 -



Preparation of 2-Amino-5-aminomethyl-6-methylpyridine dihydrochloride

- 5 A mixture of 2-amino-5-cyano-6-methylpyridine (4.0 g, 30.0 mmol) and 10% Pd/C (3.08 g) in ethanol (80 mL), methanol (30 mL), concentrated HCl (6 mL) and water (10 mL) was shaken on a Parr apparatus at 60 psi for 25 h. The reaction was filtered through celite, rinsing with 1:1 ethanol/methanol and was evaporated *in vacuo* to a solid,
- 10 which was triturated with 5:1 ethyl acetate/ethanol to give the title compound (5.95 g, 94%):
- ¹H NMR (CD₃OD): δ 2.58 (s, 3 H), 4.12 (s, 2 H), 6.92 (d, J = 9.2 Hz, 1 H), 7.93 (d, J = 9.2 Hz, 1 H).

- 43 -

Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

METHOD 4

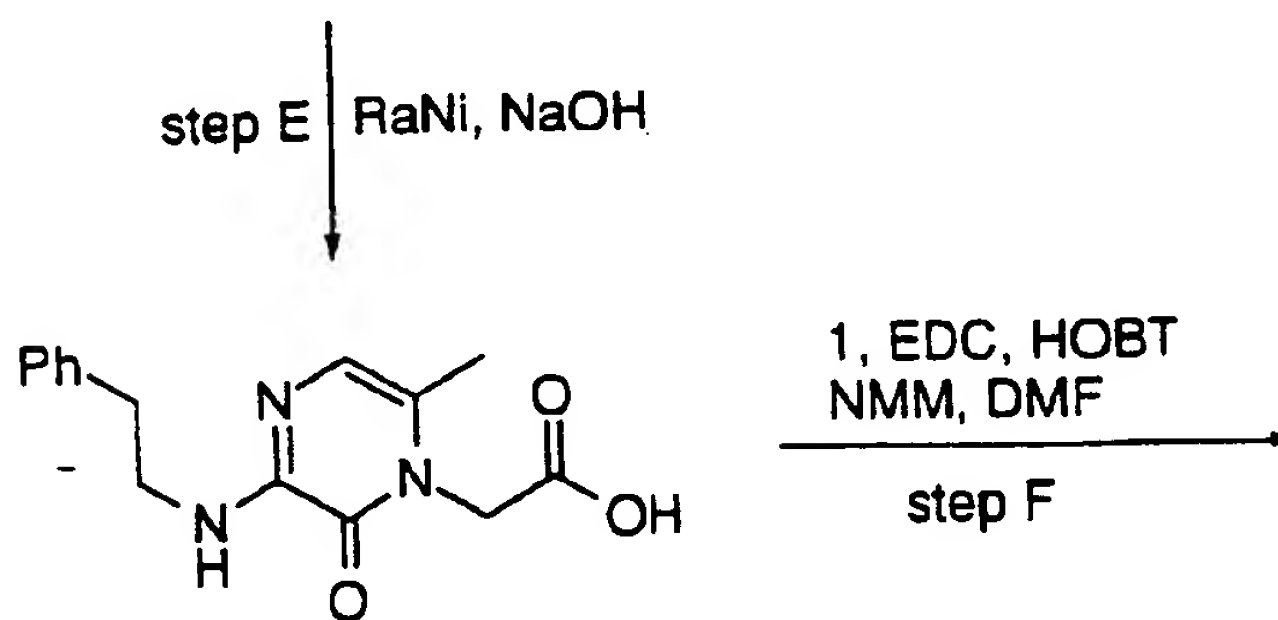
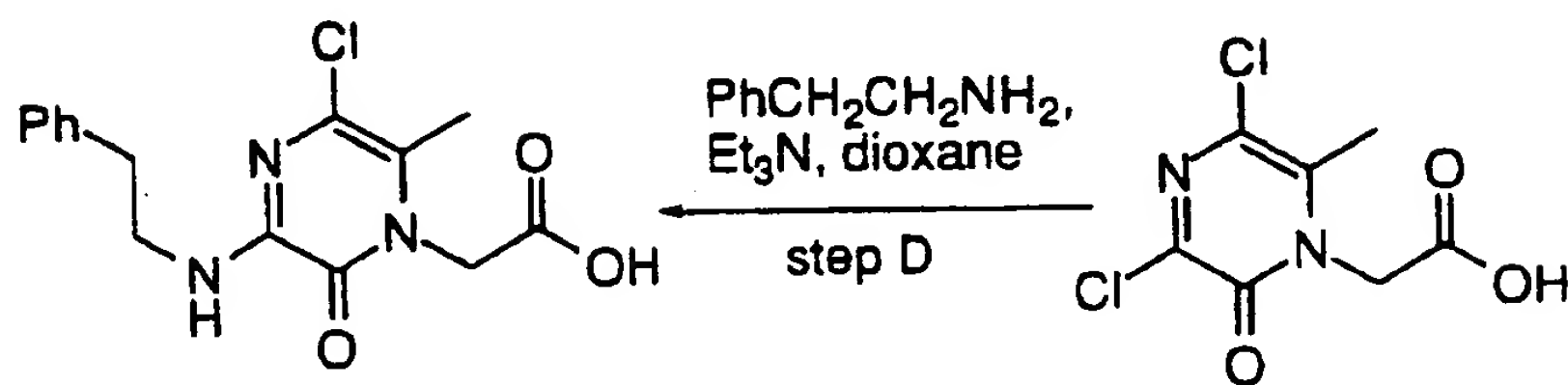
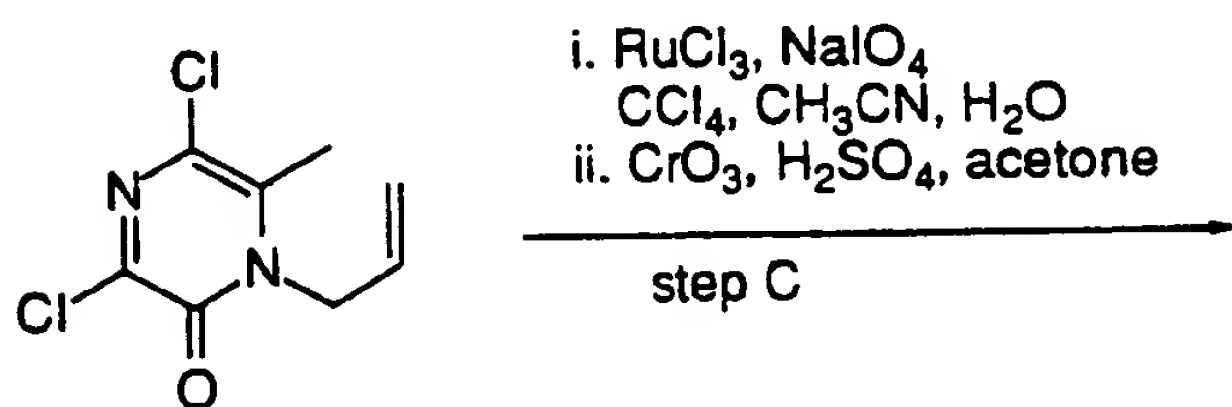
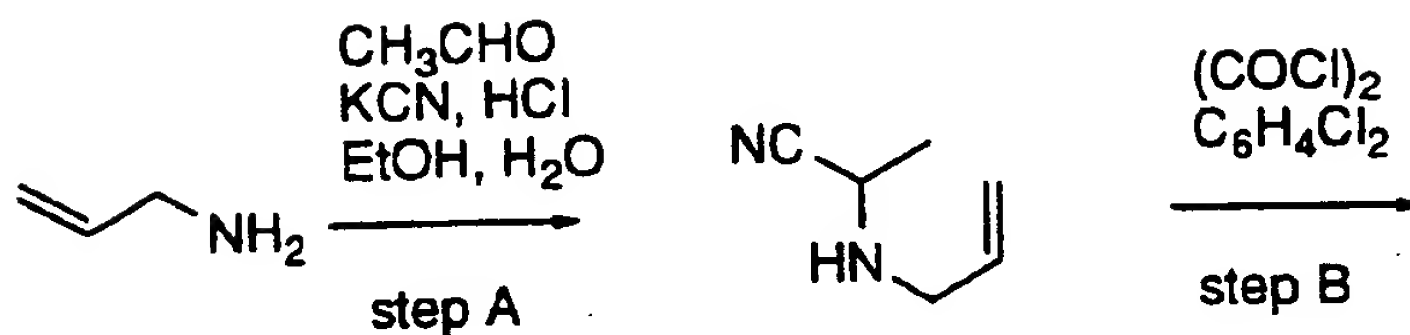
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The product of Step E, Method 3 is coupled with the appropriate protected amine, for example 2-t-butoxycarbonylamino-5-aminomethyl-6-methylpyridine, and then deprotected to afford the final product. Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

METHOD 5 (Exemplified by Example LXXXII)

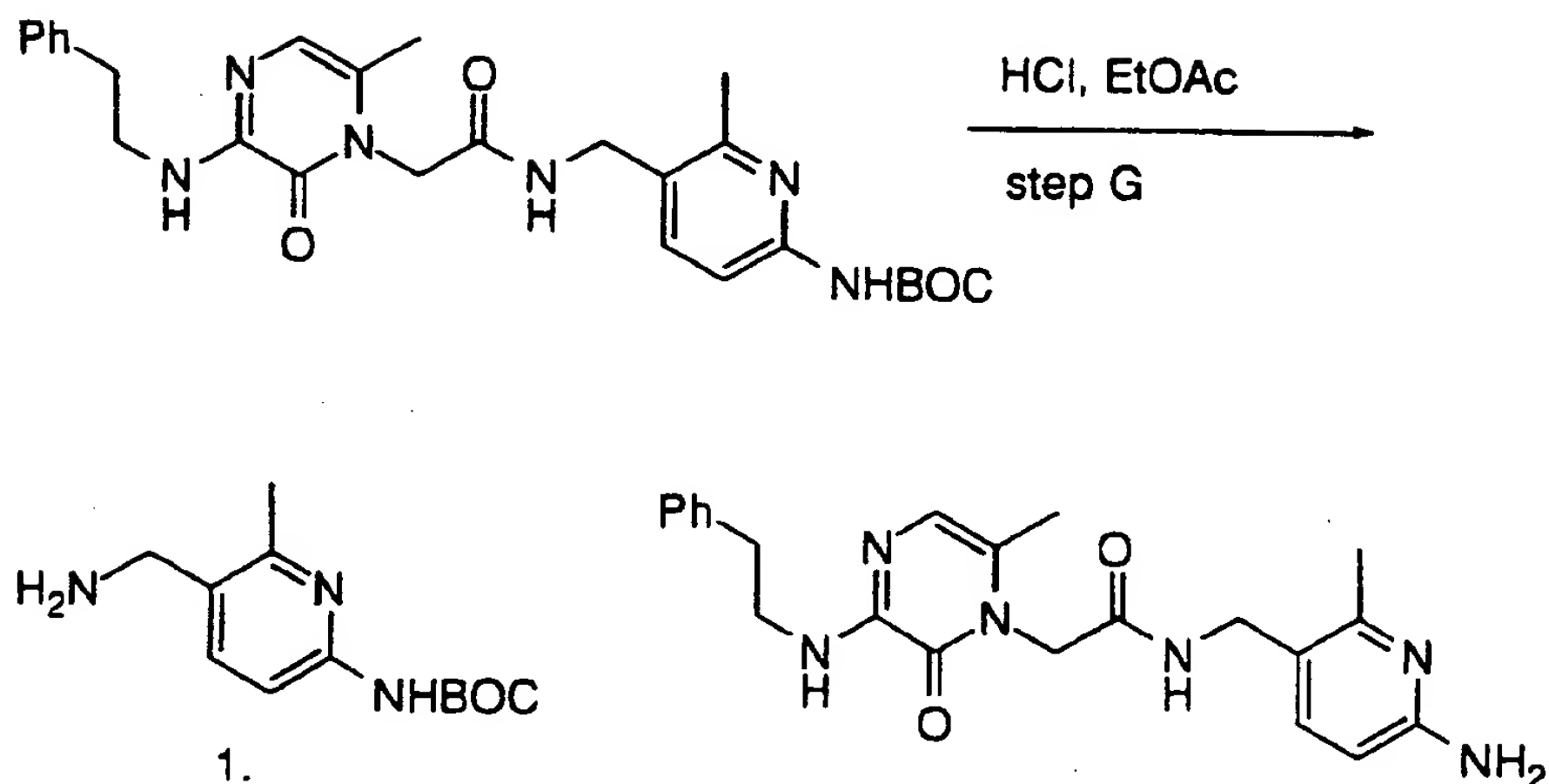
Starting allylamine is condensed with acetaldehyde and cyanide in Step A to afford the aminonitrile. This is reacted in Step B with oxalyl chloride according to the method of Hoornaert [*J. Heterocyclic Chem.*, 20, 919, (1983)] to give the pyrazinone. The olefin is oxidatively cleaved with ruthenium tetroxide and the resulting aldehyde is converted to the acid by an oxidising agent such as chromic acid in Step C. The 3-chloro group is then displaced by the appropriate amine, in this case phenethylamine, in Step D and the remaining chlorine is then removed by reduction with Raney nickel in Step E. The acid is then coupled in Step F with the appropriate amine, in this case 3-aminomethyl-6-BOC-amino-2-methylpyridine and the BOC group is removed using a strong acid such as HCl gas in step G to afford the final product.

- 44 -

METHOD 5 (CONTD)

- 45 -

METHOD 5 (CONTD)



Amide couplings, e.g., Step F, to form the compounds of this invention can be performed by the carbodiimide method with reagents such as dicyclohexylcarbodiimide, or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide. Other methods of forming the amide or peptide bond include, but are not limited to the synthetic routes via an acid chloride, azide, mixed anhydride or activated ester. Typically, solution phase amide couplings are performed, but solid-phase synthesis by classical Merrifield techniques may be employed instead. The addition and removal of one or more protecting groups is also typical practice.

15 Modifications of the method will allow different W, R³, X
and A groups contemplated by the scope of the broad claim below to be
present by the use of an appropriate reagent or appropriately substituted
starting material in the indicated synthetic step. For example the starting
aldehyde in Step A can have as its side chain, ethyl, isopropyl,
20 cyclopropyl, trifluoromethyl, and the like, to achieve the different
operable values of R³. Likewise, different W groups can be present by
the use of an appropriate amine in Step D. Different X groups can be
present by the omission of step E, and by the use of a reagent such as

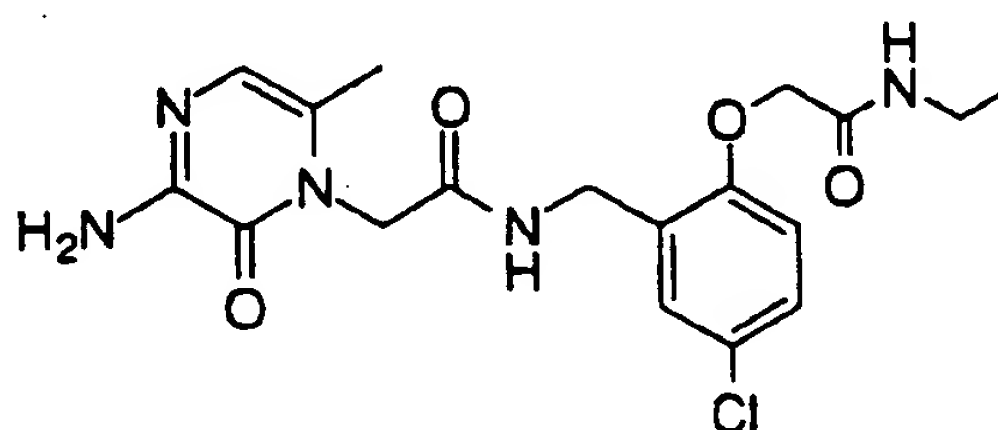
- 46 -

oxalyl bromide in step B. An appropriate choice of the amine in Step F will allow the different operable values of A to be achieved. Thus, as exemplified by Example VI, the product of Step E is coupled to derivatives of 2-hydroxybenzylamine, in this case ethyl-(2-aminomethyl-4-chlorophenoxy)-acetamide to give the final product. Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

The following examples are illustrative of the invention as contemplated by the inventors and should not be construed as being limits on the scope or spirit of the instant invention.

EXAMPLE I

Preparation of 3-Amino-6-Methyl-1-[Ethyl-(2-Methyl-carboxamidomethyl)-4-Chlorophenoxy]-Acetamido]-2-Pyrazinone



Step A: α -(Allylamino)-propionitrile hydrochloride

Concentrated HCl (20 ml, 0.24 mol) was added to a stirred solution of allylamine (36 ml, 0.48 mol) in water (100 ml) and ethanol (60 ml) at 0°C. Potassium cyanide (15 g, 0.23 mol) and acetaldehyde (11.2 ml, 0.20 mol) were then added and the mixture was heated to reflux. After 15 h the volatiles were removed *in vacuo* and the residual solution was saturated with NaCl and was extracted with methylene chloride (3 times). The combined extracts were dried (Na₂SO₄) and evaporated *in vacuo* to an oil which was dissolved in 1 M HCl (200 ml). The solution was evaporated *in vacuo*, azeotroping with 1:1 toluene/methanol to give a solid which was heated to reflux in ethyl

- 47 -

acetate (200 ml), cooled, filtered and dried to give the title compound as the HCl salt: ^1H NMR (400 MHz, CD_3OD) δ 1.72 (d, $J = 7.0$ Hz, 3H, CH_3), 3.78-3.90 (m, 2H, CH_2), 4.63 (q, $J = 7.0$ Hz, a-CH), 5.56-5.66 (m, 2H, CHCH_2), 5.91-6.02 (m, 1H, CHCH_2).

5

Step B: 1-Allyl-3,5-dichloro-6-methylpyrazinone

A stirred mixture of oxalyl chloride (30.5 ml, 0.35 mol) and α -(allylamino)-propionitrile hydrochloride (10.26 g, 70 mmol) in *o*-dichlorobenzene (100 ml) was heated to 100°C for 15 h. The solvent was evaporated *in vacuo* and the residual black oil was purified by flash column chromatography on silica (eluting with 30% ethyl acetate hexanes) to give the title compound as a tan crystalline solid: ^1H NMR (400 Mz, CDCl_3) δ 2.48 (s, 3H, CH_3), 4.75 (m, 2H, NCH_2), 5.18 (m, 1H, $\text{CHCH}_\text{A}\text{HB}$), 5.33 (m, 1H, $\text{CHCH}_\text{A}\text{HB}$), 5.85-5.92 (m, 1H, $\text{CHCH}_\text{A}\text{HB}$).

15

Step C: 3,5-Dichloro-6-methyl-1-carboxymethylpyrazinone

Ruthenium trichloride hydrate (114 mg, 0.547 mmol) was added to a stirred mixture of 1-allyl-3,5-dichloro-6-methylpyrazinone (5.45 g, 24.88 mmol) and sodium periodate (21.82 g, 0.102 mol) in water (75 ml), acetonitrile (50 ml) and carbon tetrachloride (50 ml). After 3 h the reaction mixture was extracted with methylene chloride (4 times) and the combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to a syrup. The ^1H NMR (CDCl_3) of this material showed it to be a 1:1 mixture of the acid and the aldehyde. The crude mixture was dissolved in acetone (50 ml) and Jones Reagent (2.7 M) was added until the reaction remained orange. The reaction was then extracted into ethyl acetate which was then washed with brine, dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a tan solid: ^1H NMR (400 Mz, DMSO) δ 2.41 (s, 3H, Me), 4.86 (s, 2H, CH_2).

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- 48 -

Step D: 3-(4-Methoxybenzylamino)-5-chloro-6-methyl-1-carboxymethylpyrazinone

4-Methoxybenzylamine (0.83 ml, 6.33 mmol) was added to a stirred solution of 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone (0.50 g, 2.11 mmol) in dioxane (6 ml) and the resulting mixture was warmed to 60°C. After 16 h the reaction mixture was partitioned between chloroform and 10% citric acid solution and the organic layer was dried (Na₂SO₄) and evaporated *in vacuo*. The crude product was purified by flash column chromatography (eluting with 2% methanol/chloroform/2% acetic acid) to give after azeotroping dry with toluene/methanol the title compound as a white solid:
¹H NMR (300 Mz, CD₃OD) δ 2.27 (s, 3H, CCH₃), 3.76 (s, 3H, OCH₃), 4.46 (s, 2H, CH₂), 4.87 (s, 2H, CH₂), 6.85 (d, J = 8.8 Hz, 1H, aryl H's), 7.27 (d, J = 8.8 Hz, 1H, aryl H's).

Step E: 3-(4-Methoxybenzylamino)-6-methyl-1-carboxymethylpyrazinone

Raney nickel alloy (2 g) was added to a stirred solution of 3-(4-methoxybenzylamino)-5-chloro-6-methyl-1-carboxymethylpyrazinone (448 mg, 1.33 mmol) in 1:1 methanol/1 M NaOH (50 ml). After 2 h the reaction mixture was filtered through celite, washing with 1:1 methanol/water and the filtrate was evaporated *in vacuo* to a white solid. The inorganic salts were removed by preparative HPLC (C18, water/acetonitrile/ 0.1% TFA gradient) to give the TFA salt of the title compound as a foam:
¹H NMR (300 Mz, CDCl₃) δ 2.15 (s, 3H, CCH₃), 3.81 (s, 3H, OCH₃), 4.63 (s, 4H, 2xCH₂), 6.57 (s, 1H, pyrazinone H), 6.91 (d, J = 8.7 Hz, 1H, aryl H's), 7.30 (d, J = 8.7 Hz, 1H, aryl H's).

Step F: 3-Amino-6-methyl-1-carboxymethylpyrazinone

A stirred solution of 3-(4-methoxybenzylamino)-6-methyl-1-carboxymethylpyrazinone (387 mg, 0.927 mmol) in TFA (8 ml) was heated to reflux for 6 h. The reaction was evaporated *in vacuo* azeotroping with methylene chloride and ethyl acetate. Methanol was

- 49 -

added to the crude product and the resulting solids were filtered and dried to give the TFA salt of the title compound:

¹H NMR (400 Mz, CD₃OD) δ 2.21 (s, 3H, CH₃), 4.81 (s, 2H, CH₂), 6.56 (s, 1H, pyrazinone H).

5

Step G: 3-Amino-6-Methyl-1-[Ethyl-(2-Methylcarboxamidomethyl-4-Chlorophenoxy)-Acetamido]-2-Pyrazinone

EDC Hydrochloride (67 mg, 0.35 mmol) was added to a stirred mixture of 3-amino-6-methyl-1-carboxymethylpyrazinone (80 mg, 0.27 mmol), HOBT (47 mg, 0.35 mmol), ethyl-(2-aminomethyl-4-chlorophenoxy)-acetamide (85 mg, 0.35 mmol) and N-methylmorpholine (0.11 ml, 0.97 mmol) in DMF (1 ml) and the mixture was stirred for 16 h. Water was added to the reaction and the precipitated solid was collected by filtration and dried *in vacuo*. The crude product was suspended in ethyl acetate which was then heated to reflux, cooled and filtered, to give after drying the title compound as a white crystalline solid, m.p. >200°C: ¹H NMR (300 Mz, DMSO) δ 0.97 (t, J = 7.2 Hz, 3H, CH₂CH₃), 2.02 (s, 3H, CH₃), 3.09 (quintet, J = 6.8 Hz, 2H, CH₂CH₃), 4.37 (d, J = 5.6 Hz, 2H, CONHCH₂), 4.47 (s, 2H, CH₂CO), 4.63 (s, 2H, CH₂CO), 6.30 (br s, 2H, NH₂), 6.51 (s, 1H, pyrazinone H-5), 6.94 (d, J = 9.3 Hz, 1H, phenoxy H-6), 7.28 (m, 2H, remainder), 7.98 (br t, 1H, NH), 8.67 (br t, 1H, NH); MS (FAB) 408 (M+1)⁺.

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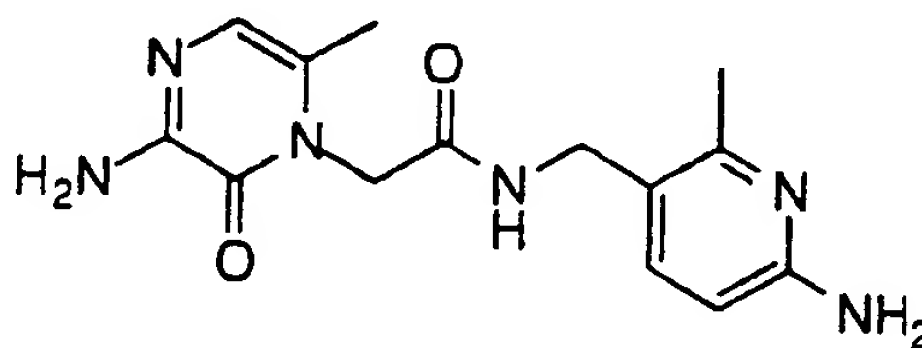
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EXAMPLE II

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Preparation of 3-Amino-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



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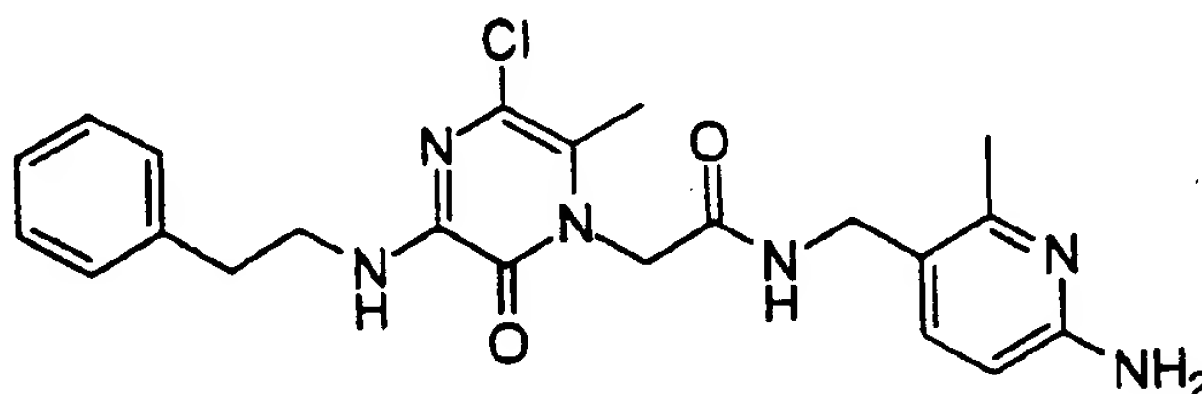
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The title compound was prepared as the HCl salt from 3-amino-6-methyl-1-carboxymethylpyrazinone and 2-amino-5-aminomethyl-6-methylpyridine dihydrochloride using the procedure of EXAMPLE 1, Step G, m.p. >200°C: MS (FAB) 303 (M+1)⁺.

5

EXAMPLE III

Preparation of 3-(2-Phenethylamino)-5-chloro-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



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Step A: 3,5-Dichloro-6-methyl-1-(2-t-butoxycarbonylamino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

EDC Hydrochloride (249 mg, 1.3 mmol) was added to a stirred mixture of 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone (237 mg, 1.0 mmol), HOBt (176 mg, 1.3 mmol), 5-aminomethyl-2-t-butoxycarbonylamino-6-methylpyridine (237 mg, 1.0 mmol) and N-methylmorpholine (0.25 ml, 2.3 mmol) in DMF (4 ml) and the mixture was stirred for 2 h. The reaction was diluted with ethyl acetate and was washed with 10% citric acid solution, water, sodium hydrogen carbonate solution and brine, dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound as a foam:

¹H NMR (400 Mz, CDCl₃) δ 1.51 (s, 9H, t-Bu), 2.39 (s, 3H, CH₃), 2.59 (s, 3H, CH₃), 4.37 (d, J = 5.5 Hz, NHCH₂), 4.71 (s, 2H, CH₂CO), 6.76 (br t, 1H, NHCH₂), 7.14 (s, 1H, NHBOC), 7.44 (d, J = 8.3 Hz, pyridine H-3), 7.66 (d, J = 8.3 Hz, pyridine H-3).

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- 51 -

Step B: 3-(2-Phenethylamino)-5-chloro-6-methyl-1-(2-t-butoxycarbonylamino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

5 Phenethylamine (0.10 ml, 0.80 mmol) was added to a stirred solution of 3,5-dichloro-6-methyl-1-(2-t-butoxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-pyrazinone (182 mg, 0.40 mmol) in dioxane (0.8 ml) and the resulting solution was warmed to 60°C. After 16 h the reaction mixture was partitioned between water and chloroform. The organic layer was dried (Na₂SO₄) and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (ethyl acetate/hexanes gradient, 40-75% ethylacetate) to give the title compound.

10 ¹H NMR (300 Mz, CDCl₃) δ 1.51 (s, 9H, t-Bu), 2.36 (s, 3H, CH₃), 2.41 (s, 3H, CH₃), 2.92 (t, J = 7.1 Hz, PhCH₂), 3.66 (q, J = 7.1 Hz, PhCH₂CH₂), 4.35 (d, J = 5.4 Hz, 2H, CONHCH₂), 4.63 (s, 2H, CH₂CO), 6.05 (br t, 1H, NH), 6.54 (br t, 1H, NH), 7.14 (s, 1H, NHBOC), 7.21-7.31 (m, 5H, Ph), 7.43 (d, J = 8.3 Hz, 1H, pyridine H-3), 7.69 (d, J = 8.3 Hz, 1H, pyridine H-4).

20 Step C: 3-(2-Phenethylamino)-5-chloro-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

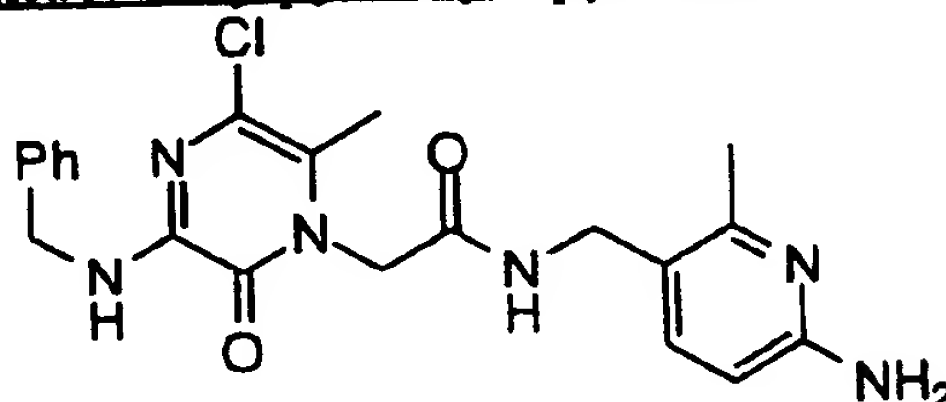
HCl gas was bubbled through a solution of 3-(2-phenethylamino)-5-chloro-6-methyl-1-(2-t-butoxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-pyrazinone (83 mg, 0.153 mmol) in ethyl acetate (10 ml) at 0°C for 10 min. The reaction was warmed to r.t. and after 1 h the solution was degassed with argon to give a white precipitate which was collected by filtration and dried to give the title compound as the HCl salt.

30 ¹H NMR (400 Mz, CD₃OD) δ 2.26 (s, 3H, CH₃), 2.50 (s, 3H, CH₃), 2.91 (t, J = 7.0 Hz, PhCH₂), 3.60 (t, J = 7.0 Hz, PhCH₂CH₂), 4.29 (s, 2H, CONHCH₂), 4.74 (s, 2H, CH₂CO), 6.82 (d, J = 9.0 Hz, 1H, pyridine H-3), 7.18-7.29 (m, 5H, Ph), 7.83 (d, J = 9.0 Hz, 1H, pyridine H-4); MS (FAB) 441 (M+1)⁺.

- 52 -

EXAMPLE IV

Preparation of 3-Benzylamino-5-chloro-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

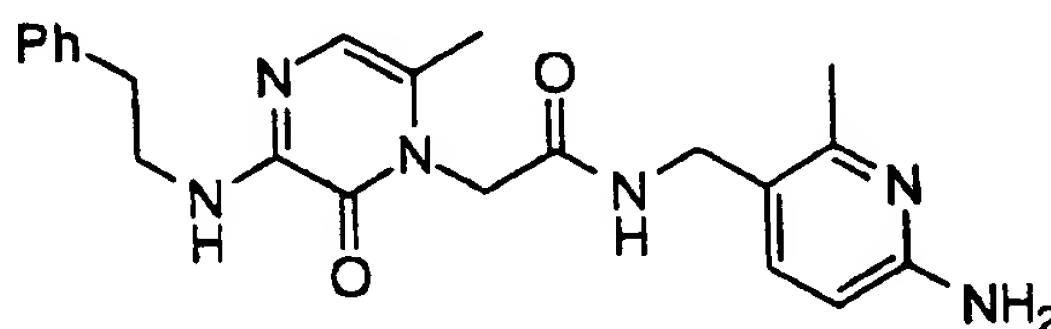


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The title compound was prepared as the TFA salt from 3,5-dichloro-6-methyl-1-(2-t-butoxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-pyrazinone and benzylamine using the procedure of EXAMPLE III, Steps B and C: MS (FAB) 428 (M+1)⁺.

EXAMPLE V

15 Preparation of 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



20 Step A: Benzyl-N-(1-cyanoethyl)glycine hydrochloride
TMSCN (18.8 mL, 141 mmol) was added cautiously (the reaction is exothermic) to a stirred solution of benzylglycine free base (23.3 g, 141 mmol - from the HCl salt by partition between EtOAc and brine basified with saturated Na₂CO₃ solution) and acetaldehyde (7.88 mL, 141 mmol) in methylene chloride (50 mL). After 4 h the volatiles
25 were removed *in vacuo* and the residue was taken up in EtOAc and was

- 53 -

washed with brine, dried (Na₂SO₄) and evaporated *in vacuo* to an oil. The oil was redissolved in EtOAc and 9.9 M HCl in EtOH (15.25 mL, 151 mmol) was added to give a crystalline precipitate which was isolated by filtration, washing with EtOAc and Et₂O to give the title compound:

5 ¹H NMR (CD₃OD): d 1.70 (d, J = 7.0 Hz, 3H, CH₃), 4.16 (d, J = 16.8 Hz, 1H, CH_AH_B), 4.21 (d, J = 16.8 Hz, 1H, CH_AH_B), 4.64 (q, J = 7.0 Hz, a-CH), 5.31 (s, 2H, CH₂O), 7.35-7.44 (m, 5H, Ph).

10 Step B: 1-Benzylloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone

A stirred mixture of oxalyl chloride (40.4 mL, 463 mmol) and benzyl-N-(1-cyanoethyl)glycine hydrochloride (29.51 g, 116 mmol) in 1,2-dichlorobenzene (110 mL) was heated to 100° C for 15 h. The volatiles were evaporated *in vacuo* and the residue was purified by flash column chromatography on silica (eluting with hexanes followed by 30% ethyl acetate/hexanes) to give a solid which was heated to reflux in 2:5 EtOAc/hexanes (140 mL), cooled, and collected by filtration to give the title compound as a pale green crystalline solid:

15 ¹H NMR (CDCl₃): d 2.35 (s, 3H, CH₃), 4.88 (s, 2H, CH₂), 5.24 (s, 2H, CH₂), 7.38 (m, 5H, Ph).

20 Step C: 3-(2-Phenethylamino)-5-chloro-6-methyl-1-(benzyloxycarbonylmethyl)-pyrazinone

Phenethylamine (15.07 mL, 120 mmol) was added to a stirred mixture of 1-benzylloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone (13.09 g, 40 mmol) in EtOAc (80 mL) and the resulting mixture was heated to reflux under argon. After 2 h the reaction was cooled, diluted with chloroform (500 mL) and washed with 5% citric acid solution and brine, dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound as a crystalline solid:

30 ¹H NMR (CDCl₃): d 2.21 (s, 3H, CH₃), 2.93 (t, J = 7.1 Hz, 2H, PhCH₂), 3.67 (q, J = 6.7 Hz, 2H, CH₂NH), 4.79 (s, 2H, CH₂), 5.21 (s, 2H, CH₂), 6.10 (br t, 1H, NH), 7.20-7.39 (m, 10H, 2Ph).

- 54 -

Step D: 3-(2-Phenethylamino)-5-chloro-6-methyl-1-carboxymethylpyrazinone

LiOH.H₂O (3.36 g, 80 mmol) was added to a stirred suspension of the product from Step C in 3:3:1 THF/MeOH/H₂O (280 mL) at 0° C and the mixture was warmed to RT. After 16 h the volatiles were evaporated *in vacuo* and the solution was diluted with water (500 mL) and was washed with EtOAc. The aqueous layer was saturated with NaCl and acidified with 20% KHSO₄ solution (20 mL) to give a precipitate which was extracted into 1:1 ethyl acetate/THF (400 mL). The organic layer was dried (Na₂SO₄) and evaporated *in vacuo* to a solid which was heated to reflux in 1:1 ethyl acetate/hexanes, cooled and collected by filtration to give the title compound as a crystalline solid: ¹H NMR (DMSO-d₆): d 2.21 (s, 3H, Me), 2.86 (t, J = 7.4 Hz, 2H, PhCH₂), 3.47 (dt, J = 5.9 and 7.4 Hz, 2H, CH₂NH), 4.72 (s, 2H, CH₂CO₂), 7.18-7.31 (m, 5H, Ph), 7.46 (t, J = 5.9 Hz, 1H, NH), 13.30 (br s, 1H, COOH).

Step E: 3-(2-Phenethylamino)-6-methyl-1-carboxymethylpyrazinone
3-(2-Phenethylamino)-5-chloro-6-methyl-1-

carboxymethylpyrazinone (11.66 g, 36.2 mmol) was added to a stirred solution of potassium hydroxide (86% by weight, 6.10 g, 93.5 mmol) in water (400 mL). After degassing the resulting solution with argon, 10% Pd/C (3.48 g) was added and the mixture was stirred under a hydrogen filled balloon. After 16 h, the mixture was degassed with nitrogen, more 10% Pd/C (3.0 g) was added and the mixture was stirred under a hydrogen filled balloon for a further 7 h, filtered through celite, washing the cake with water (200 mL). The filtrate was acidified with a solution of KHSO₄ (7.8 g, 57.3 mmol) in water (35 mL) and the resulting precipitate was collected by filtration, washing with water (200 mL), and was dried for 16 h *in vacuo* to give the title compound as a crystalline solid: ¹H NMR (DMSO-d₆): d 2.07 (d, J = 0.7 Hz, 3H, Me), 2.84 (t, J = 7.4 Hz, 2H, PhCH₂), 3.47 (dt, J = 5.9 and 7.4 Hz, 2H, CH₂NH), 4.66 (s, 2H,

- 55 -

CH₂CO₂), 6.67 (s, 1H, pyrazinone H-5), 6.88 (br t, J = 5.9 Hz, 1H, NH), 7.17-7.32 (m, 5H, Ph).

Step F: 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

EDC.HCl (0.962 g, 5.02 mmol) was added to a stirred mixture of 3-(2-phenethylamino)-6-methyl-1-carboxymethylpyrazinone (1.20 g, 4.18 mmol), 2-amino-5-aminomethyl-6-methylpyridine dihydrochloride (0.874 g, 4.16 mmol), HOBT.H₂O (0.678 g, 5.02 mmol) and N-methylmorpholine (2.30 mL, 20.9 mmol) in dry DMF (10 mL). After 16 h, the volatiles were evaporated *in vacuo* and the residue was partitioned between ethyl acetate and 1M HCl solution. The aqueous layer was adjusted to pH 10 with saturated sodium carbonate solution and the precipitate was collected by filtration, washing with water and ethanol to give the title compound as the free base.

The free base material was used as a starting material to form 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride (Step G1), 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride Type A monohydrate (Step G2, also referred to as "polymorphic crystalline form Type A monohydrate") or 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride Type B monohydrate (Step G3, also referred to as "polymorphic crystalline form Type B monohydrate").

In general, production of 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride Type A monohydrate comprises the steps of a) dissolving 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone in acetic acid solvent and adding aqueous HCl; b) recovering the resultant solid phase; and c) removing the solvent therefrom. In one aspect of this process, the amount

- 56 -

of aqueous HCl added in step a) is such that the final water content in the acetic acid is between 1 and 5 weight %.

In general, production of 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride Type B monohydrate comprises the steps of a) dissolving 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone in hydrochloric acid solvent; b) recovering the resultant solid phase; and c) removing the solvent therefrom.

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Step G1 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride

15 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone free base was suspended in ethanol (20 mL) and ethanolic HCl (9.9M, 8.36 mmol) was added with stirring at 0° C. The bis-HCl salt rapidly crystallizes from the mixture and after 30 min it was collected by filtration, washing with ethanol, and was dried for 16 h at 0.5 mm Hg to give the title compound;

20 ¹H NMR (DMSO-d₆): δ 2.10 (s, 3H, CH₃), 2.45 (s, 3H, CH₃), 2.91 (t, J = 7.6 Hz, PhCH₂), 3.63 (br q, CH₂NH), 4.17 (d, J = 5.5 Hz, 2H, CONHCH₂), 4.62 (s, 2H, CH₂CO), 6.68 (s, 1H, pyrazinone H-5), 6.81 (d, J = 9.0 Hz, 1H, pyridine H-3), 7.21-7.31 (m, 5H, Ph), 7.76 (obscured d, 1H, pyridine H-4), 7.77 (br s, 2H, NH₂), 8.81 (br t, J = 5.5 Hz, 1H, CONH).

25

Step G2 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride Type A monohydrate

30 3-(2-phenethyl-amino)-6-methyl-1-(2-amino-6-methyl-5-methylene-carboxamidomethylpyridinyl)-pyrazinone free base (680 g) was dissolved in 6.0 L of acetic acid and the mixture was stirred with warming to 60°C to obtain a solution. The mixture was filtered and the filter flushed with 7.6 L of acetic acid and aqueous HCl (734 mL 5 N HCl

- 57 -

and 147 mL water) was added to the cooled solution at 28°C. The mixture was seeded and warmed to 73°C to give a fine seed bed, then cooled to 20°C over several h and filtered and the filter cake washed with acetic acid followed by 190 proof ethanol and dried at 60°C in the vacuum oven with a nitrogen purge to give the title compound.

The Type A compound is characterized by a differential scanning calorimetry (DSC) curve, at a heating rate of 5°C/min in an open cup under flowing nitrogen bubbled through water at 5°C exhibiting an endotherm with an extrapolated onset temperature of about 102°C, a peak temperature of about 112°C and an associated heat of about 115J/gm followed by an endotherm with an extrapolated onset temperature of about 171°C, a peak temperature of about 194°C and an associated heat of about 83J/gm. The low temperature endotherm is due to the loss of the water of hydration and the high temperature endotherm is due to melting with decomposition of the remaining anhydrous phase. The x-ray powder diffraction pattern is characterized by d-spacings of 13.06, 12.16, 7.40, 5.71, 4.92, 4.48, 4.40, 3.63, 3.07, 2.98, 2.86 and 2.62Å.

20 Step G3 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone
dihydrochloride Type B monohydrate

A 100 liter vessel was charged with 8.12 liters of 2 N hydrochloric acid (HCl), followed by the addition of 1.62 liters of DI water, at ambient temperature. To the vessel was added 3-(2-phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylene-carboxamidomethylpyridinyl)-pyrazinone free base (3.30 kg) and the contents were heated to 82°C. After aging for 15 minutes, Solka flok (24 g) was added and the resulting solution was filtered via residual vacuum through consecutive line filters (20 and 5 micron). The original vessel was rinsed with 3.25 liters of DI water (ambient temperature), which was combined with the original filtrate and reheated to 72°C. The solution was cooled to 53°C, seeded, and the cooling continued to 25°C over 3 hours. Concentrated hydrochloric acid (1.30 liters) was added dropwise

- 58 -

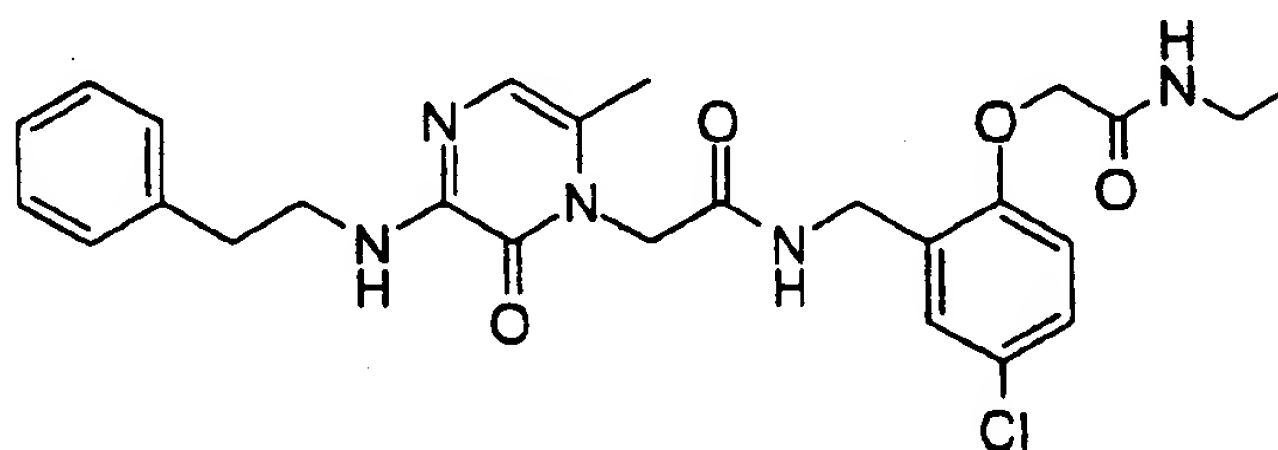
over 30 minutes to the slurry. The slurry was cooled to 20°C and the solids isolated via vacuum filtration. The cake was washed with 6.48 liters of 1 N HCl. The cake was then washed with ethanol (190 proof; 3 x 6.48 liters). The wet cake was dried in vacuo at ambient temperature to give the title compound.

The Type B compound is characterized by a differential scanning calorimetry (DSC) curve, at a heating rate of 5°C/min in an open cup under flowing nitrogen bubbled through water at 5°C exhibiting an endotherm with an extrapolated onset temperature of about 120°C, a peak temperature of about 132°C, and an associated heat of about 123J/gm followed by an endotherm with an extrapolated onset temperature of about 160°C, a peak temperature of about 191°C and an associated heat of about 78J/gm. The low temperature endotherm is due to the loss of the water of hydration and the high temperature endotherm is due to melting with decomposition of the remaining anhydrous phase. The x-ray powder diffraction pattern is characterized by d-spacings of 12.98, 11.91, 7.24, 5.98, 4.90, 4.46, 4.23, 3.99, 3.75, 3.61, 3.41, 2.94, 2.85 and 2.61 Å.

20

EXAMPLE VI

3-(2-Phenethylamino)-6-Methyl-1-[Ethyl-(2-Methylcarboxamidomethyl-4-Chlorophenoxy)-Acetamidol-2-Pyrazinone



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EDC Hydrochloride (56 mg, 0.29 mmol) was added to a stirred mixture of 3-(2-phenethylamino)-6-methyl-1-carboxymethylpyrazinone (91 mg, 0.23 mmol), HOBT (40 mg, 0.29 mmol), ethyl-(2-aminomethyl-4-chlorophenoxy)-acetamide hydrochloride (82 mg, 0.29 mmol) and N-methylmorpholine (0.13 ml,

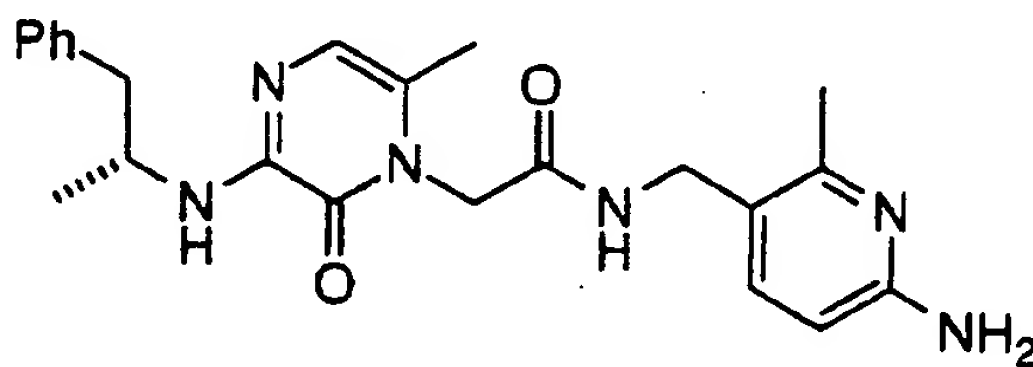
- 59 -

1.17 mmol) in DMF (1 ml) and the mixture was stirred for 16 h. The reaction was partitioned between ethyl acetate and water, adding sufficient brine to disperse the emulsion. The cloudy organic layer was collected and the solids dissolved by adding chloroform and methanol, and the solution was dried and evaporated to a solid. The crude product was suspended in ethyl acetate and filtered, washing with water followed by ethyl acetate to give after drying the title compound as a white crystalline solid, m.p. >200°C:

¹H NMR (400 Mz, DMSO) δ 0.97 (t, J = 7.2 Hz, 3H, CH₂CH₃), 2.03 (s, 3H, CH₃), 2.83 (t, J = 7.4 Hz, 2H, PhCH₂), 3.09 (quintet, J = 6.7 Hz, 2H, CH₂CH₃), 3.47 (q, J = 6.9 Hz, 2H, PhCH₂CH₂), 4.37 (d, J = 5.7 Hz, 2H, CONHCH₂), 4.64 (s, 2H, CH₂CO), 6.63 (s, 1H, pyrazinone H-5), 6.77 (br t, 1H, NH), 6.94 (d, J = 8.4 Hz, 1H, phenoxy H-6), 7.16-7.30 (m, 7H, remainder), 7.98 (br t, 1H, NH), 8.67 (br t, 1H, NH); MS (FAB) 512 (M+1)⁺.

EXAMPLE VII

Preparation of [R]-3-(1-Phenyl-2-propylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

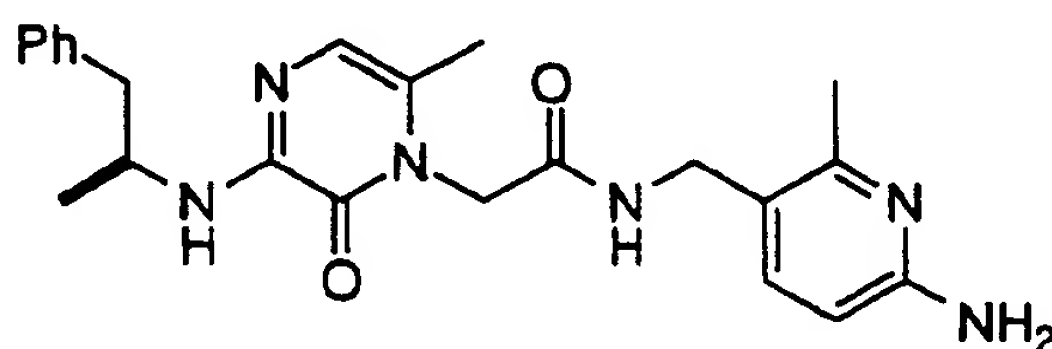


The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and [R]-1-phenyl-2-propylamine using the procedure of EXAMPLE V, Steps C-F: MS (FAB) 421 (M+1)⁺.

- 60 -

EXAMPLE VIII

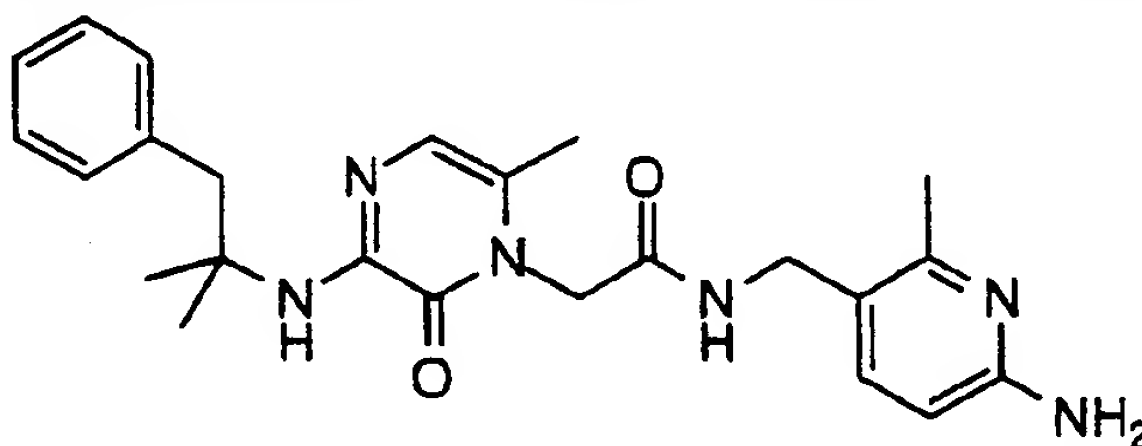
Preparation of [S]-3-(1-Phenyl-2-propylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and [S]-1-phenyl-2-propylamine using the procedure of EXAMPLE V, Steps C-F: MS (FAB) 421 (M+1)⁺.

EXAMPLE IX

Preparation of 3-(1-Phenyl-2-methyl-2-propylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

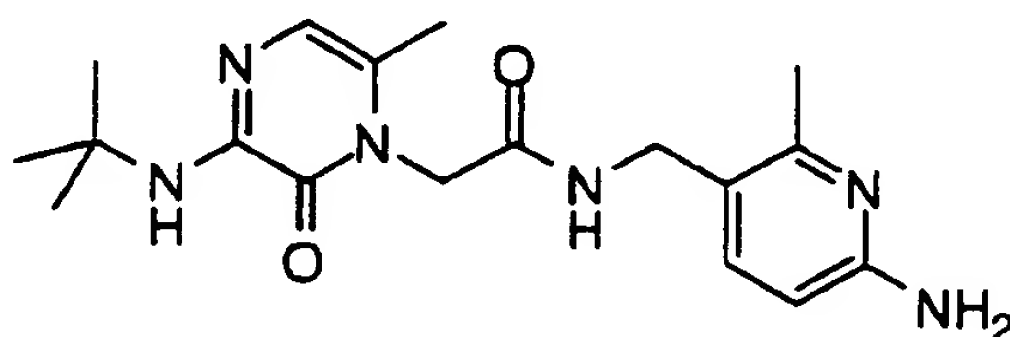


The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 1-phenyl-2-methyl-2-propylamine using the procedure of EXAMPLE V, Steps C-F: MS (FAB) 435 (M+1)⁺.

- 61 -

EXAMPLE X

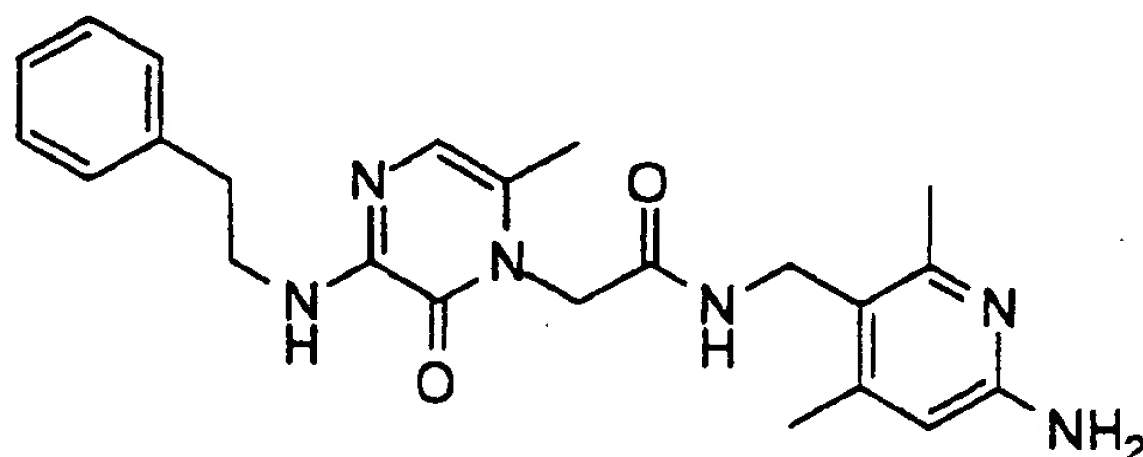
Preparation of 3-(2-Methyl-2-propylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-methyl-2-propylamine using the procedure of EXAMPLE V, Steps C-F: MS (FAB) 358 (M+1)⁺.

EXAMPLE XI

Preparation of 3-(2-Phenethylamino)-6-methyl-1-(2-amino-4,6-dimethyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

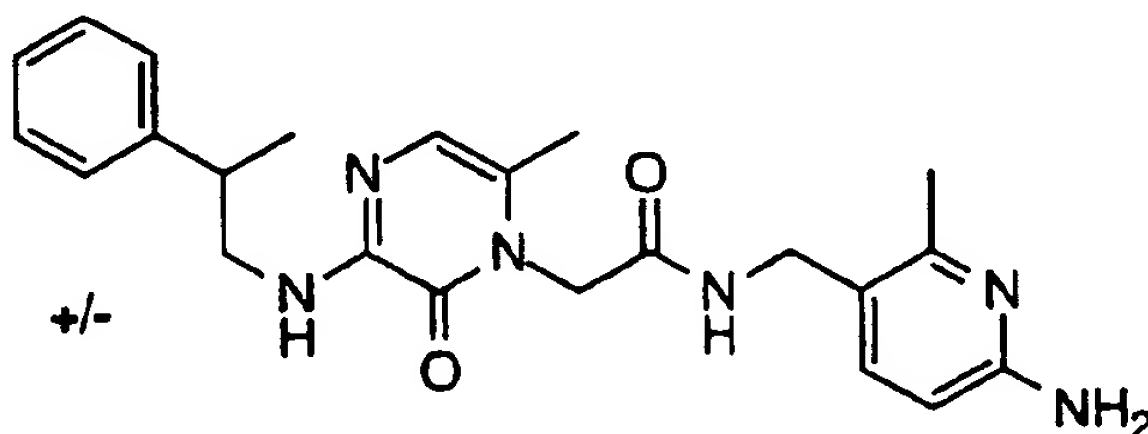


The title compound was prepared as the HCl salt from 3-(2-phenethylamino)-6-methyl-1-methylcarboxypyrazinone and 2-amino-5-aminomethyl-4,6-dimethylpyridine dihydrochloride using the procedure of EXAMPLE V, Step F, m.p. >200° C: MS (FAB) 421 (M+1)⁺.

- 62 -

EXAMPLE XII

Preparation of [R,S]-3-(2-Phenyl-1-propylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

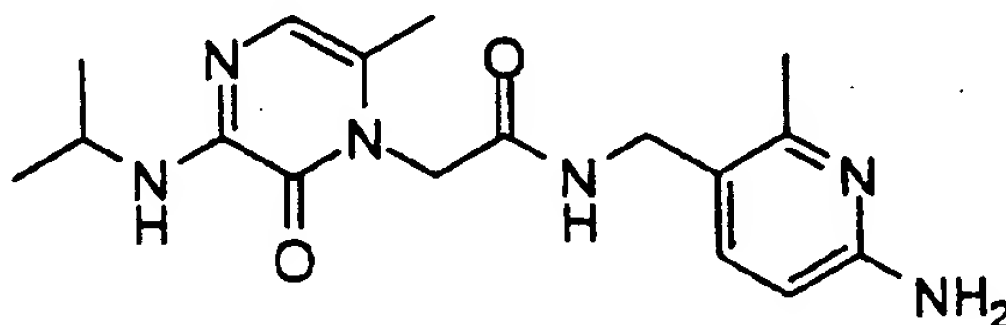


The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and rac-2-phenyl-1-propylamine using the procedure of EXAMPLE V, Steps C-F, m.p. >200° C: MS (FAB) 421 (M+1)⁺.

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EXAMPLE XIII

Preparation of 3-(2-Propylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



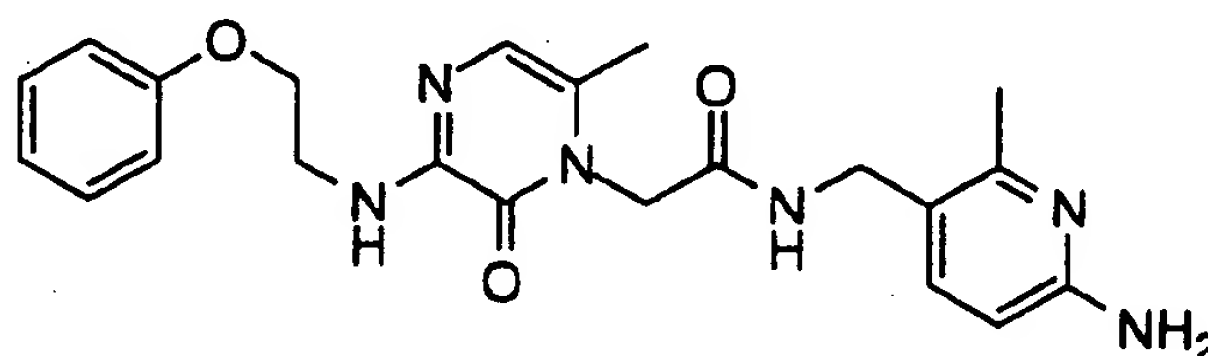
The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-propylamine using the procedure of EXAMPLE V, Steps C-F, m.p. >200° C: MS (FAB) 345 (M+1)⁺.

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- 63 -

EXAMPLE XIV

Preparation of 3-(2-Phenoxyethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



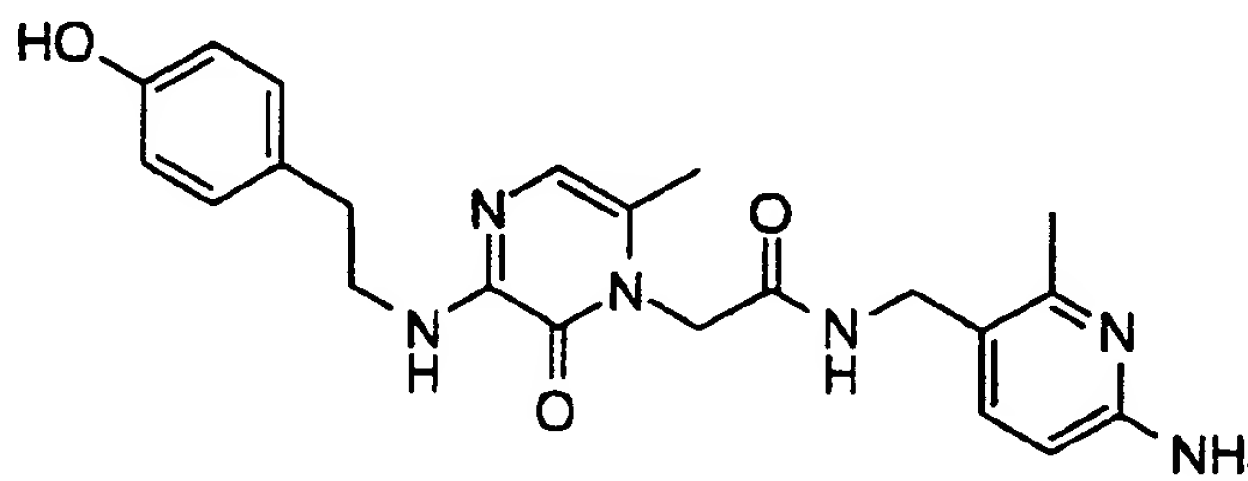
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The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-phenoxyethylamine using the procedure of EXAMPLE V, Steps C-F, m.p. >200°C: MS (FAB) 423 (M+1)⁺.

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EXAMPLE XV

Preparation of 3-[2-(4-Hydroxyphenyl)-ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



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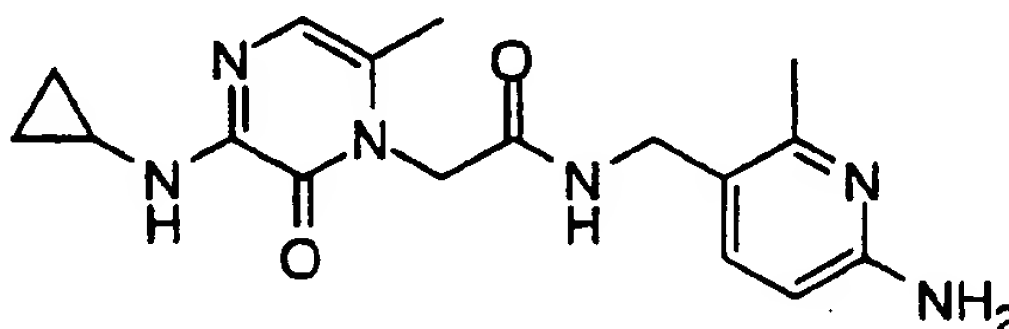
The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-(4-hydroxyphenyl)-ethylamine using the procedure of EXAMPLE V, Steps C-F, m.p. 195-199°C: MS (FAB) 423 (M+1)⁺.

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- 64 -

EXAMPLE XVI

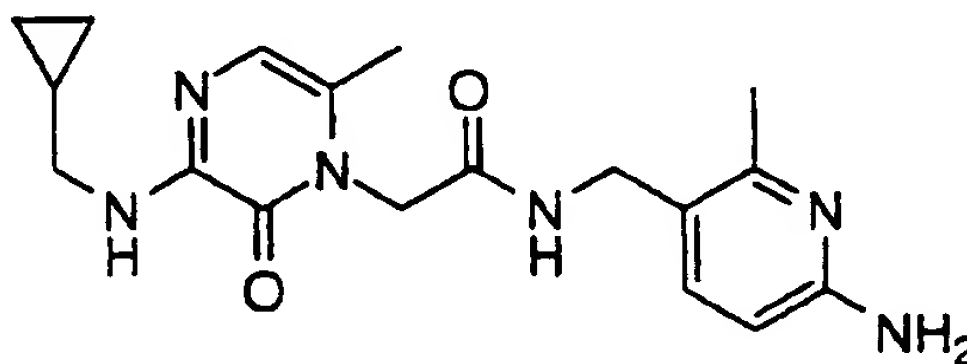
Preparation of 3-Cyclopropylamino-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



The title compound was prepared as the TFA salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and cyclopropylamine using the procedure of EXAMPLE V, Steps C-F: MS (FAB) 343 (M+1)⁺.

EXAMPLE XVII

Preparation of 3-Cyclopropylmethylamino-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

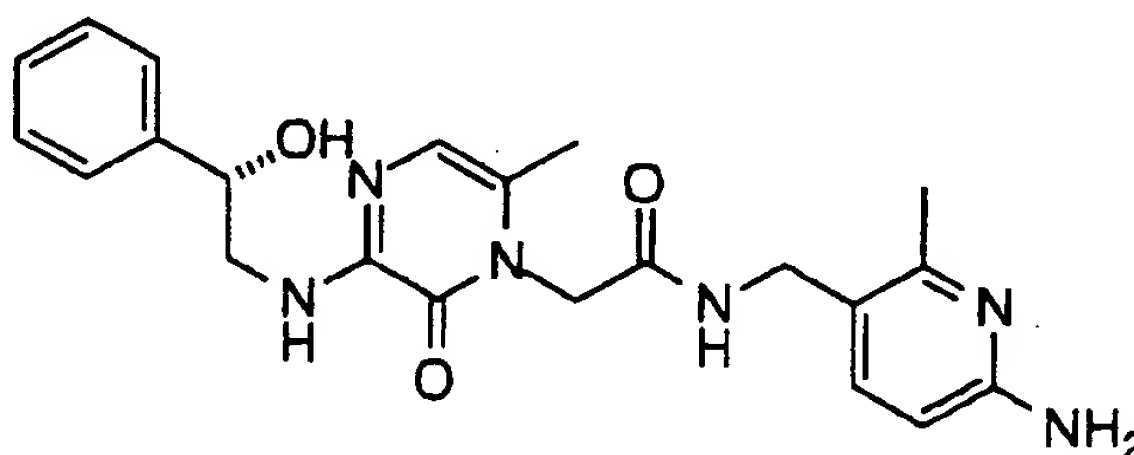


The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and cyclopropylmethylamine using the procedure of EXAMPLE V, Steps C-F, m.p. >200° C: MS (FAB) 357 (M+1)⁺.

- 65 -

EXAMPLE XVIII

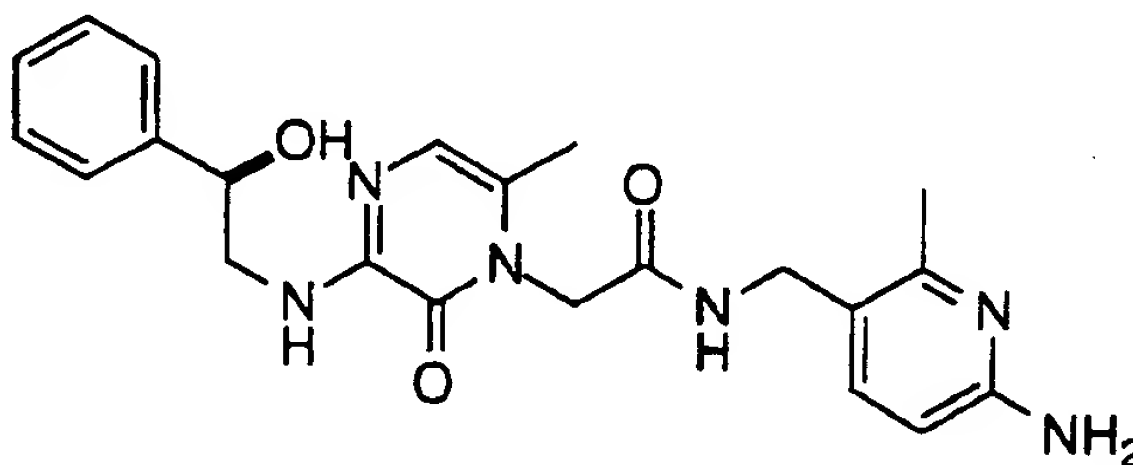
Preparation of [S]-3-(2-Hydroxy-2-phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and [S]-2-hydroxyphenethylamine using the procedure of EXAMPLE V, Steps C-F, m.p. >200°C: MS (FAB) 423 (M+1)⁺.

EXAMPLE XIX

Preparation of [R]-3-(2-Hydroxy-2-phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

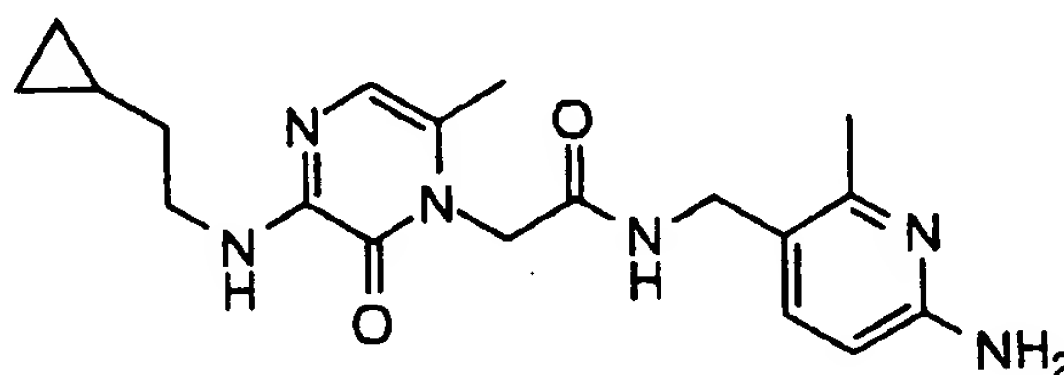


The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and [R]-2-hydroxyphenethylamine using the procedure of EXAMPLE V, Steps C-F: MS (FAB) 423 (M+1)⁺.

- 66 -

EXAMPLE XX

Preparation of 3-(2-Cyclopropylethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



5

Step A: 4-Phthalimido-1-butene

A mixture of 4-bromo-1-butene (1.01 mL, 10.0 mmol) and potassium phthalimide (1.85 g, 10.0 mmol) in DMF (10 mL) was stirred at 100°C for 3 h. The resulting mixture was cooled and partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried (Na₂SO₄) and evaporated *in vacuo* to a crystalline solid. The crude product was purified by flash column chromatography on silica (eluting with 20% ethyl acetate/hexanes) to give the title compound as a crystalline solid:

¹H NMR (300 Mz, CDCl₃) δ 2.45 (q, J = 7.0 Hz, 2H), 3.78 (t, J = 7.0 Hz, 2H), 5.04 (m, 2H), 5.76 (m, 1H), 7.71 (m, 2H), 7.84 (m, 2H).

15

Step B: 2-Phthalimidoethylcyclopropane

4-Phthalimido-1-butene was cyclopropanated using the procedure of Suda (*Synthesis*, 1981, 714) to give the title compound as a crystalline solid:

¹H NMR (400 Mz, CDCl₃) δ 0.05 (m, 2H), 0.42 (m, 2H), 0.69 (m, 1H), 1.58 (q, J = 7.1 Hz, 2H), 3.77 (t, J = 7.1 Hz, 2H), 7.71 (m, 2H), 7.84 (m, 2H).

25

- 67 -

Step C: 2-Cyclopropylethylamine

A mixture of 2-phthalimidoethylcyclopropane (1.40 g, 6.50 mmol) and hydrazine hydrate (0.32 mL, 6.50 mmol) in ethanol (10 mL) was stirred at reflux for 1 h. The mixture was cooled and cHCl (0.54 mL, 6.50 mmol) was added to give a thick precipitate. The mixture was evaporated in vacuo and the residue was suspended in 1 M HCl solution (10 mL) and warmed to 50°C for 5 min, cooled and filtered. The filtrate was washed with methylene chloride and then was evaporated *in vacuo*, azeotroping with toluene/ethanol to give the HCl salt of the title compound as a crystalline solid:

¹H NMR (400 Mz, CD₃OD) δ 0.15 (m, 2H), 0.54 (m, 2H), 0.74 (m, 1H), 1.55 (q, J = 7.3 Hz, 2H), 3.01 (t, J = 7.3 Hz, 2H).

Step D: 3-(2-Cyclopropylethylamino)-5-chloro-6-methyl-1-(benzyloxycarbonylmethyl)-pyrazinone

A mixture of 2-cyclopropylethylamine hydrochloride (73 mg, 0.60 mmol), 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone (164 mg, 0.50 mmol) and sodium hydrogen carbonate (101 mg, 1.20 mmol) in toluene (1 mL) and water (0.5 mL) was stirred at 80° C for 3 h. The reaction was then cooled and partitioned between methylene chloride and 10% citric acid solution. The organic layer was dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound as a crystalline solid:

¹H NMR (400 MHz, CDCl₃): δ 0.10 (m, 2H), 0.47 (m, 2H), 0.74 (m, 1H), 1.53 (q, J = 7.0 Hz, 2H), 2.21 (s, 3H, CH₃), 3.49 (q, J = 6.6 Hz, 2H), 4.80 (s, 2H), 5.22 (s, 2H), 6.18 (br t, 1H), 7.33-7.40 (m, 5H).

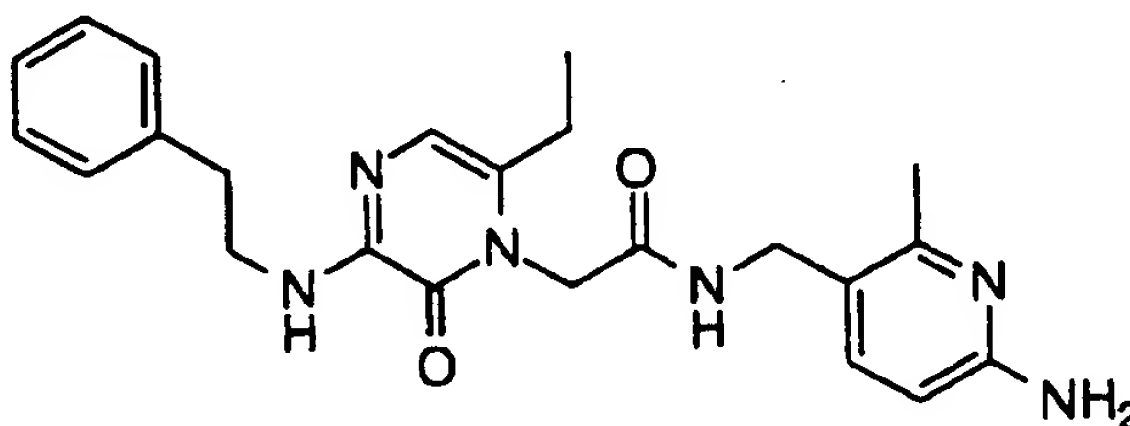
Step E: 3-(2-Cyclopropylethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

The title compound was from 3-(2-cyclopropylethylamino)-5-chloro-6-methyl-1-(benzyloxycarbonylmethyl)-pyrazinone using the procedure of EXAMPLE V, Steps D-F, m.p. >200°C: MS (FAB) 371 (M+1)⁺.

- 68 -

EXAMPLE XXI

Preparation of 3-(2-Phenethylamino)-6-ethyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



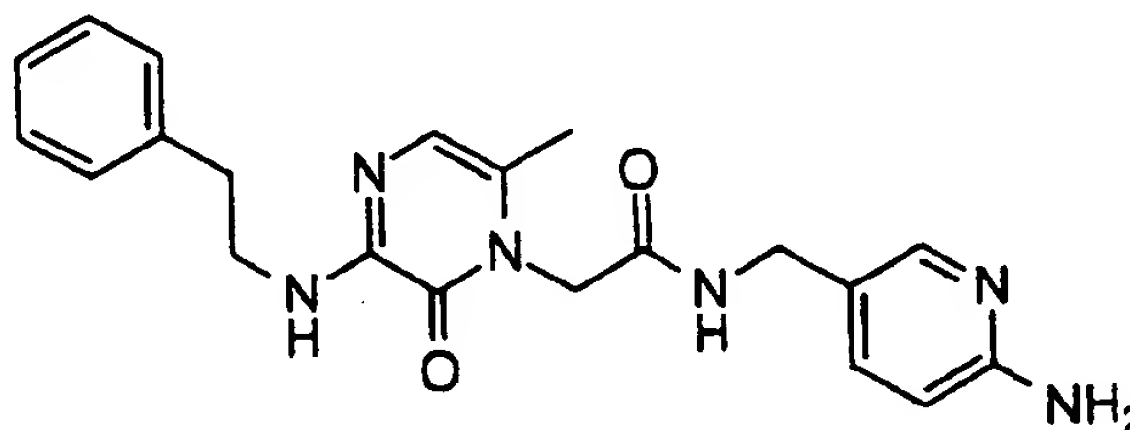
5

The title compound was prepared as the HCl salt from propionaldehyde using the procedure of EXAMPLE V: MS (FAB) 421 (M+1)⁺.

10

EXAMPLE XXII

Preparation of 3-(2-Phenethylamino)-6-methyl-1-(2-amino-5-methylcarboxamidomethylpyridinyl)-pyrazinone



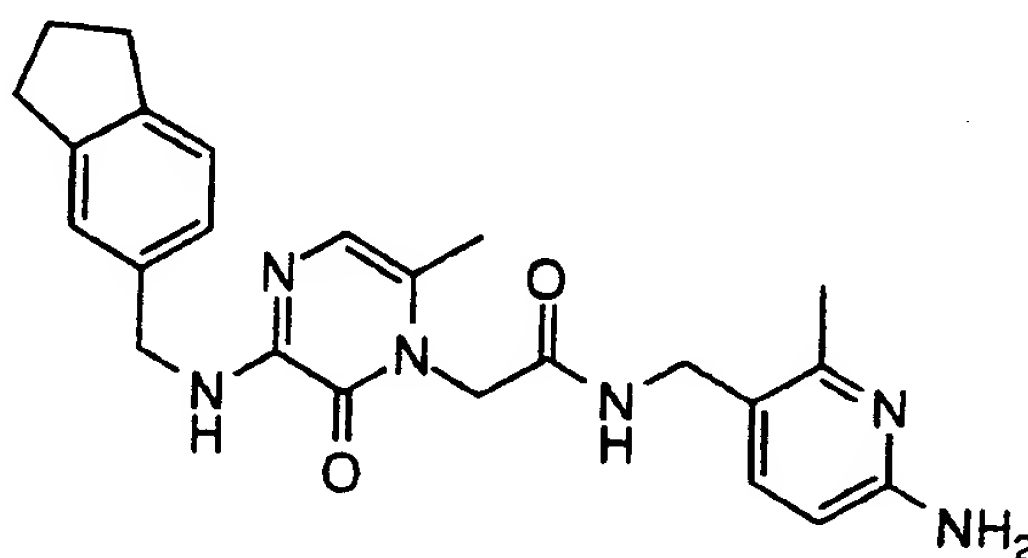
15

The title compound was prepared as the HCl salt from 3-(2-phenethylamino)-6-methyl-1-carboxymethylpyrazinone and 2-amino-5-aminomethylpyridine using the procedure of EXAMPLE V, Step F, m.p. >220°C: MS (FAB) 393 (M+1)⁺.

- 69 -

EXAMPLE XXIII

Preparation of 3-(5-Indanylmethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



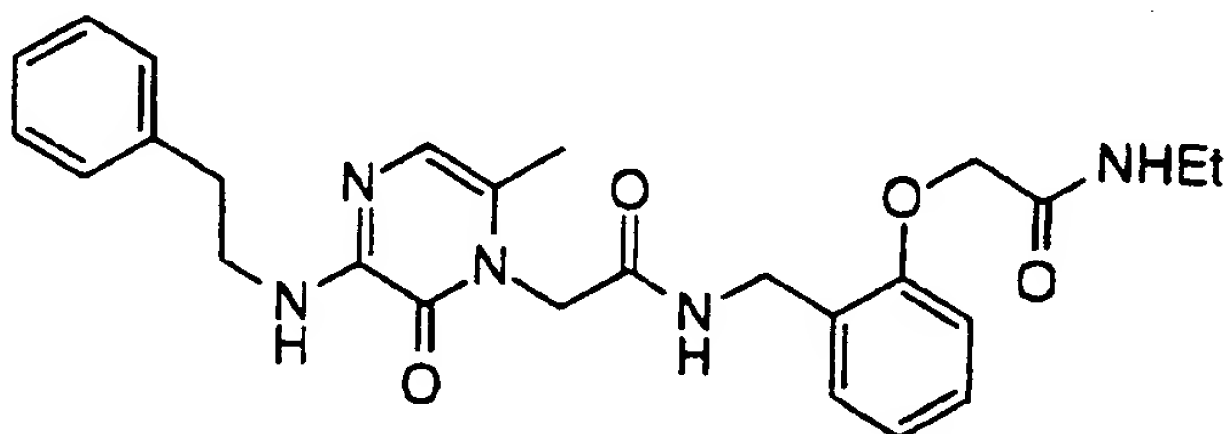
5

The title compound was prepared as the TFA salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 5-indanylmethylamine using the procedure of EXAMPLE V, Steps C-F: MS (FAB) 434 (M+1)⁺.

10

EXAMPLE XXIV

Preparation of 3-(2-Phenethylamino)-6-methyl-1-[Ethyl-(2-Methylcarboxamidomethylphenoxy)-Acetamido]-pyrazinone



15

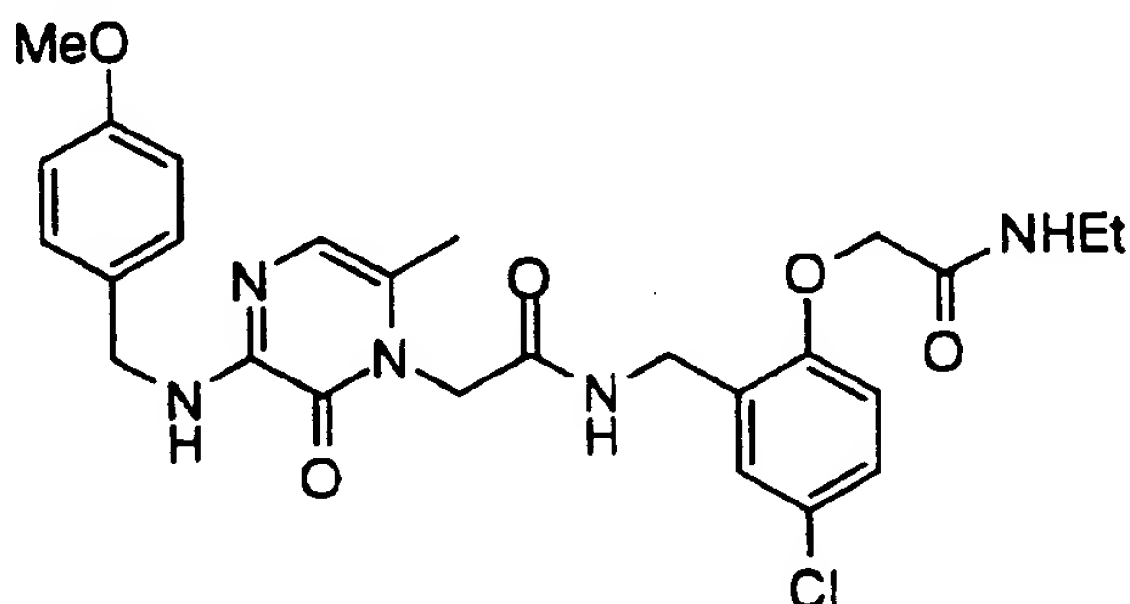
The title compound was prepared from 3-(2-phenethylamino)-6-methyl-1-carboxymethylpyrazinone and ethyl-2-aminomethylphenoxyacetamide using the procedure of EXAMPLE VI: MS (FAB) 478 (M+1)⁺.

20

- 70 -

EXAMPLE XXV

Preparation of 3-(4-Methoxybenzylamino)-6-methyl-1-[Ethyl-(2-Methylcarboxamidomethyl-4-chlorophenoxy)-Acetamido]-pyrazinone



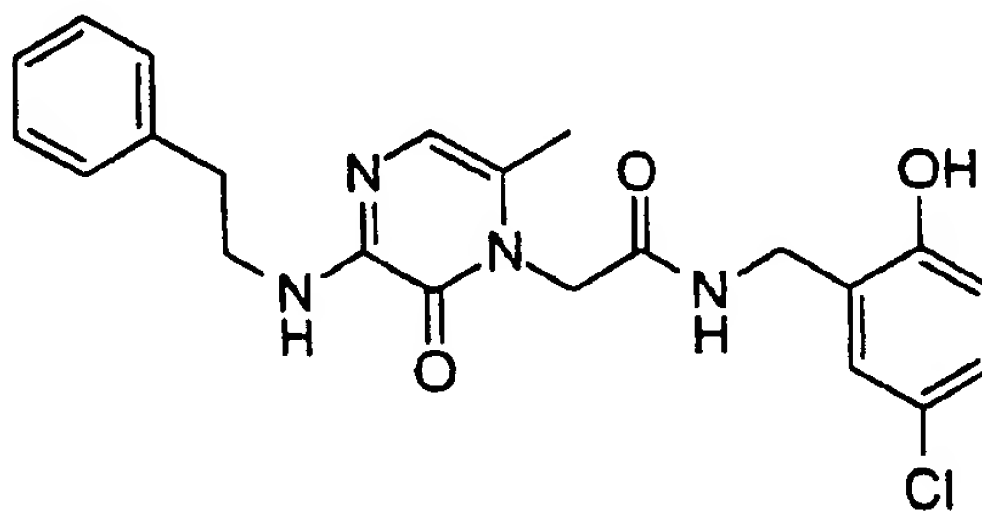
5

The title compound was prepared from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 4-methoxybenzylamine using the procedure of EXAMPLE V, Steps C-E, followed by the procedure of EXAMPLE VI, m.p. >200°C: MS (FAB)

10 528 (M+1)⁺.EXAMPLE XXVI

Preparation of 3-(2-Phenethylamino)-6-methyl-1-(Methylcarboxamidomethyl-2-hydroxy-5-chlorophenyl)-pyrazinone

15



The title compound was prepared from 3-(2-phenethylamino)-6-methyl-1-carboxymethylpyrazinone and 2-

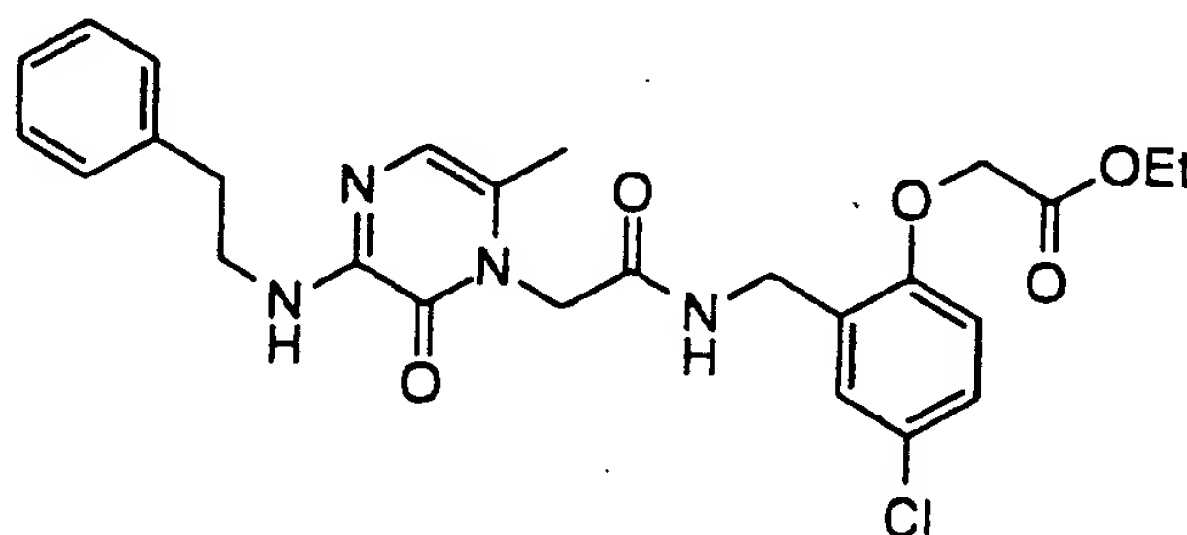
- 71 -

aminomethyl-4-chlorophenol using the procedure of EXAMPLE VI: MS (FAB) 427 (M+1)⁺.

EXAMPLE XXVII

5

Preparation of 3-(2-Phenethylamino)-6-methyl-1-[Ethyl-(2-Methylcarboxamidomethyl-4-chlorophenoxy)-Acetyl]-pyrazinone

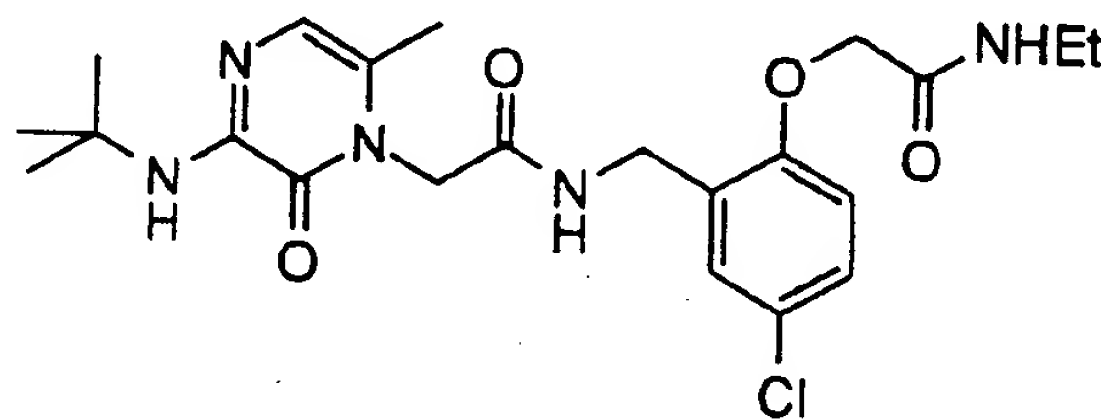


10 The title compound was prepared from 3-(2-phenethylamino)-6-methyl-1-carboxymethylpyrazinone and ethyl-2-aminomethylmethyl-4-chlorophenoxyacetate using the procedure of EXAMPLE VI: MS (FAB) 513 (M+1)⁺.

EXAMPLE XXVIII

15

Preparation of 3-(2-Methyl-2-propylamino)-6-methyl-1-[Ethyl-(2-Methylcarboxamidomethyl-4-chlorophenoxy)-Acetamido]-pyrazinone

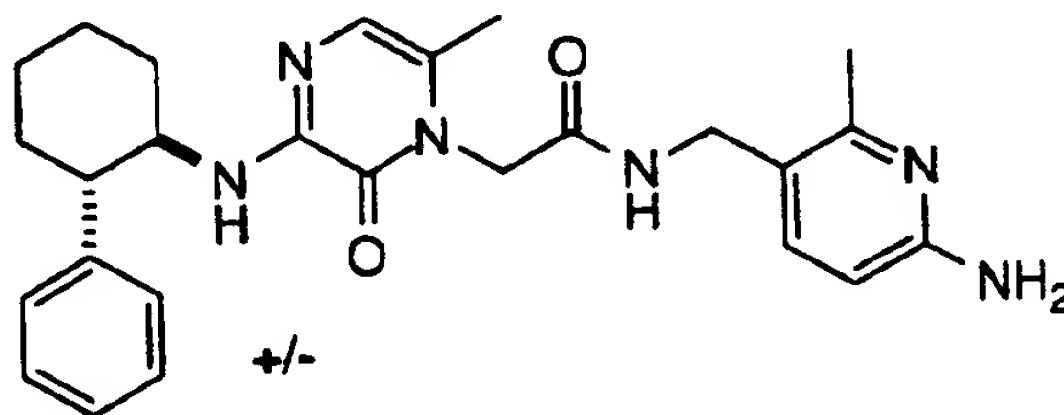


20 The title compound was prepared as the TFA salt from 3-(2-methyl-2-propylamino)-6-methyl-1-carboxymethylpyrazinone using the procedure of EXAMPLE VI, m.p. 64-70°C: MS (FAB) 464 (M+1)⁺.

- 72 -

EXAMPLE XXIX

Preparation of rac-trans-3-(2-Phenylcyclohexylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



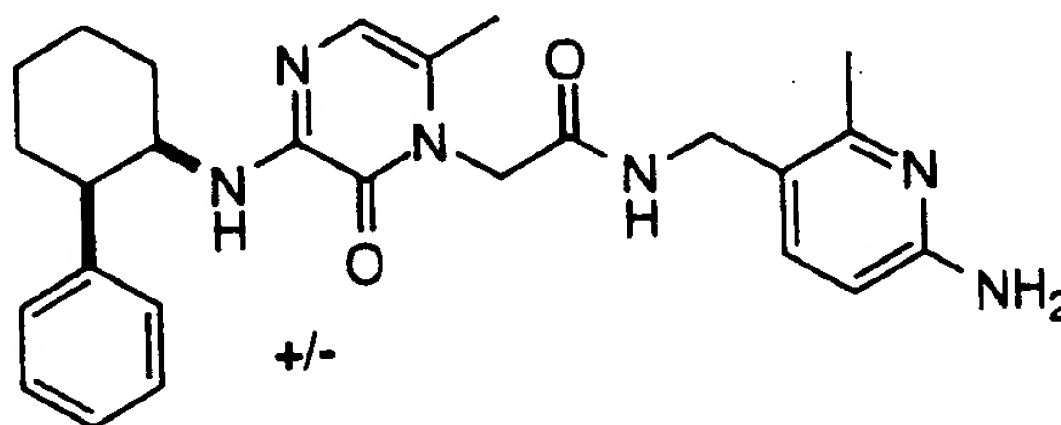
The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and rac-trans-2-phenylcyclohexylamine using the procedure of EXAMPLE V, Steps C-E, followed by the procedures of METHOD 4: MS (FAB) 461 (M+1)⁺.

10

EXAMPLE XXX

Preparation of rac-cis-3-(2-Phenylcyclohexylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

15

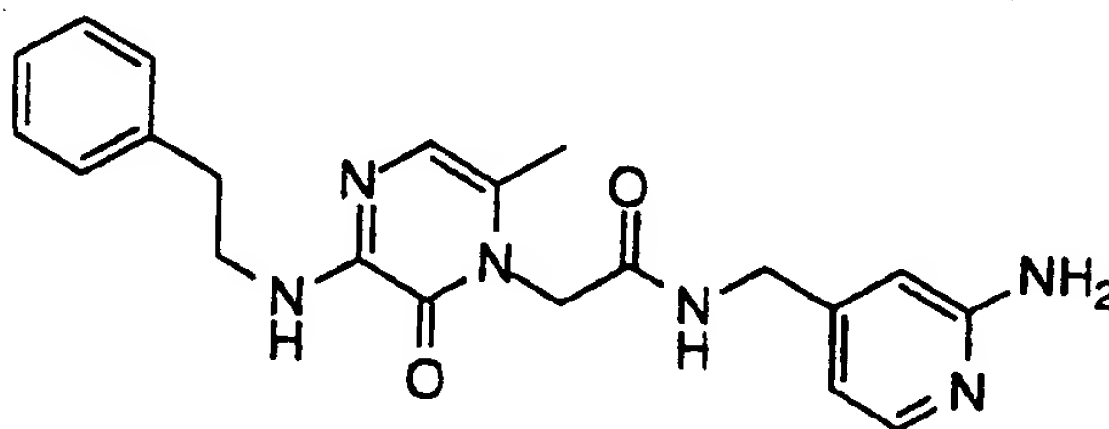


The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and rac-cis-2-phenylcyclohexylamine using the procedure of EXAMPLE V, Steps C-E, followed by the procedures of METHOD 4: MS (FAB) 461 (M+1)⁺.

- 73 -

EXAMPLE XXXI

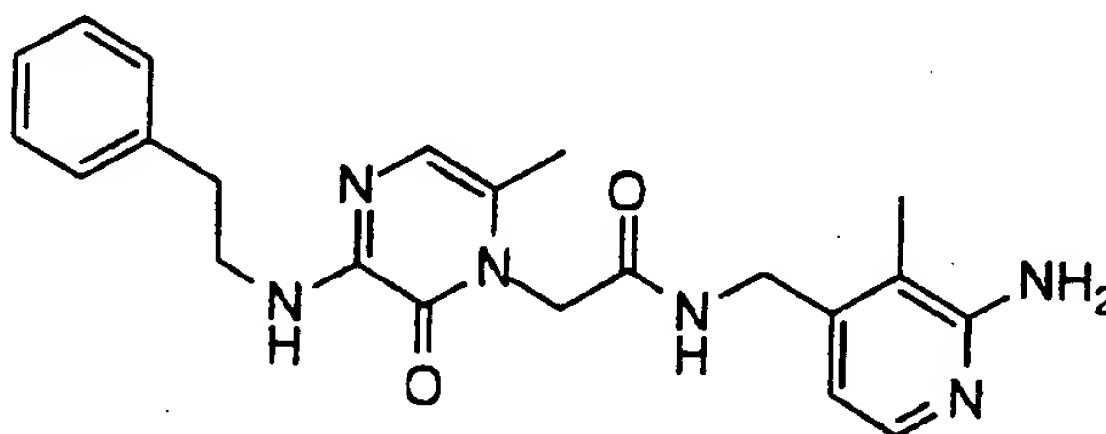
Preparation of 3-(2-Phenethylamino)-6-methyl-1-(2-amino-4-methylcarboxamidomethylpyridinyl)-pyrazinone



The title compound was prepared as the HCl salt from 3-(2-phenethylamino)-6-methyl-1-methylcarboxypyrazinone and 2-amino-4-aminomethylpyridine using the procedure of EXAMPLE V, Step F: MS (FAB) 393 (M+1)+.

EXAMPLE XXXII

Preparation of 3-(2-Phenethylamino)-6-methyl-1-(2-amino-3-methyl-4-methylcarboxamidomethylpyridinyl)-pyrazinone



Step A: 2-t-Butyloxycarbonylamino-3-methylpyridine-N-oxide

To a 0°C solution of 1.0 g (4.8 mmol) of 2-t-butyloxycarbonylamino-3-methylpyridine in 25 mL of CH₂Cl₂, was added 25 mL of 5% NaHCO₃. Five portions of 1.73 g (5 mmol) of 3-chloroperoxybenzoic acid were added over a 20 min period to the rapidly stirred mixture. The cold bath was allowed to expire overnight, and the reaction mixture quenched with 10% Na₂SO₃. After stirring for 5 min, the aqueous layer was extracted with CH₂Cl₂, dried over Na₂SO₄, treated with activated

- 74 -

carbon and the solvents removed to give an oil that was chromatographed on 50 g fine SiO₂ using 98:2 to 96:4 CHCl₃-CH₃OH to give the title compound as an off-white solid:

¹H NMR (CDCl₃) δ 8.23 (s, 1H), 8.12 (d, 1H, 6.6 Hz), 7.15 (d, 1H, 6.8 Hz),
5 6.98 (t, 1H, 6.3 Hz), 2.36 (s, 3H), 1.52 (s, 9H).

Step B: 2-t-Butyloxycarbonylamino-3-methyl-1-methoxy-pyridinium methyl sulfate

To a stirred solution of 620 mg (0.29 mmol) of 2-t-
10 butyloxycarbonylamino-3-methylpyridine-N-oxide in 8 mL of CH₂Cl₂ under Ar was added 262 μL (0.3 mmol) of dimethyl sulfate. The CH₂Cl₂ was allowed to evaporate under a slow stream of Ar overnight to give the title compound as a light tan solid:

¹H NMR (DMSO-d₆) δ 10.8 (s, 1H), 9.32 (d, 1H, 6.6 Hz), 8.50 (d, 1H, 7.8
15 Hz), 7.98 (t, 1H, 7.1 Hz), 4.28 (s, 3H), 3.37 (s, 3H), 2.41 (s, 3H), 1.49 (s, 9H).

Step C: 2-t-Butyloxycarbonylamino-4-cyano-3-methylpyridine

The product from the previous reaction was heated with 651 mg
(10 mmol) potassium cyanide in 4.5 mL of water at 50°C overnight. The
20 reaction was diluted with water and 10% Na₂CO₃, extracted with 3 x CHCl₃, the combined organic layers were washed with brine, dried over Na₂SO₄ and the solvents removed to give a dark oil that was dissolved in CHCl₃ and applied to a column of 20 g fine SiO₂. The column was eluted with 1:4 - 1:3 EtOAc-hexane to give the title compound as a colorless solid:

¹H NMR (CDCl₃) δ 7.64 (d, 1H, 7.7 Hz), 7.44 (d, 1H, 7.7 Hz), 6.80 (s, 1H),
25 2.38 (s, 3H), 1.52 (s, 9H).

Step D: 4-Aminomethyl-2-t-butyloxycarbonylamino-3-methylpyridine

A solution of 175 mg (0.75 mmol) of 2-t-butyloxycarbonylamino-
30 4-cyano-3-methylpyridine and 88 μL (1.5 mmol) of acetic acid in 10 mL of MeOH was hydrogenated over 75 mg of 10% Pd-C at 55 psi overnight on a Parr apparatus. The catalyst was removed by filtration, concentrated at reduced pressure, and the residue partitioned between CHCl₃ and 10% Na₂CO₃. The aqueous layer was extracted with CHCl₃ and the combined organic layers were

- 75 -

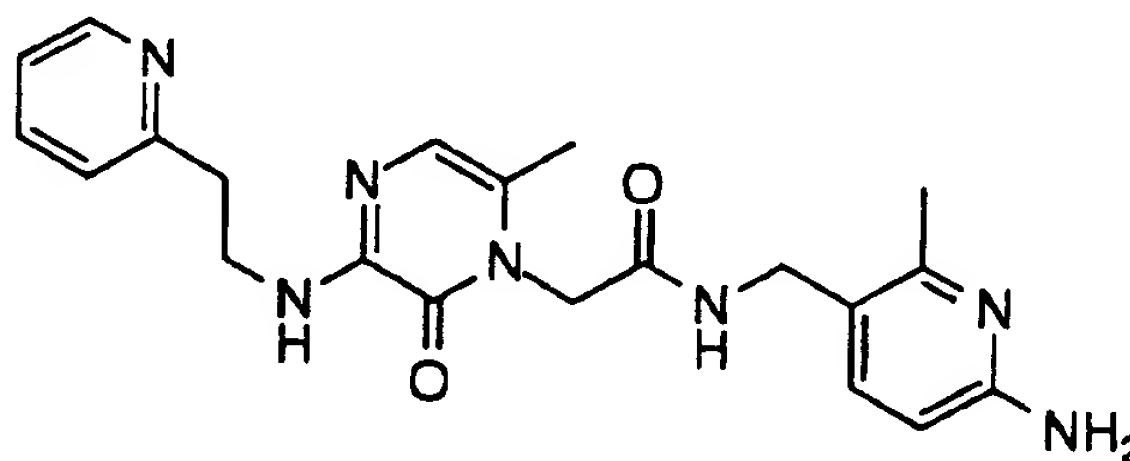
dried over Na₂SO₄ and concentrated to give 150 mg of the title compound as a colorless oil: ¹H NMR (CDCl₃) δ 7.48 (d, 1H, 7.7 Hz), 7.02 (d, 1H, 7.7 Hz), 6.69 (s, 1H), 3.88 (s, 2H), 2.28 (s, 3H), 1.51 (s, 9H).

5 Step E: 3-(2-Phenethylamino)-6-methyl-1-(2-amino-3-methyl-4-methylcarboxamidomethylpyridinyl)-pyrazinone

10 The title compound was prepared as the TFA salt from 3-(2-phenethylamino)-6-methyl-1-carboxymethylpyrazinone and 4-aminomethyl-2-t-butyloxycarbonylamino-3-methylpyridine using the procedure of METHOD 4: MS (FAB) 407 (M+1)⁺.

EXAMPLE XXXIII

15 Preparation of 3-[2-(2-Pyridyl)ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

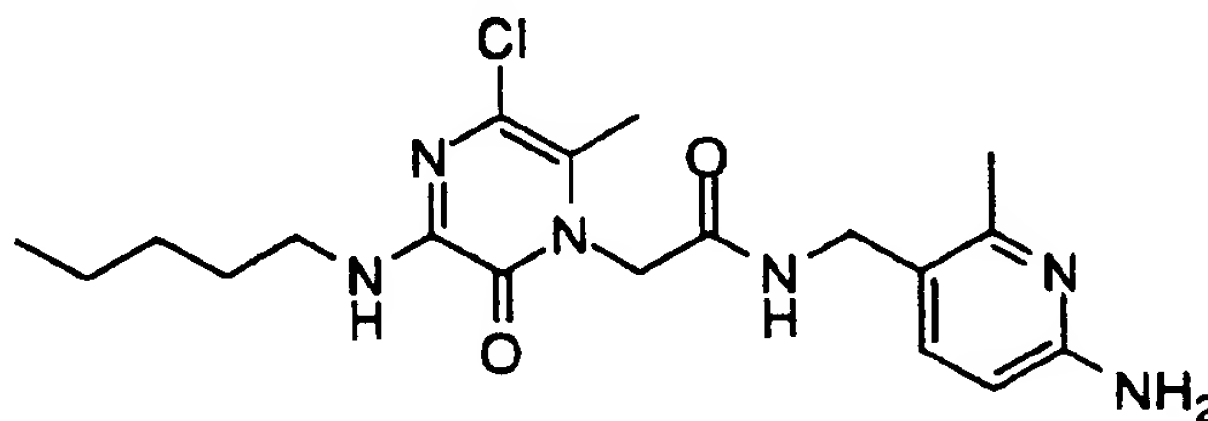


20 The title compound was prepared as the HCl salt from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and 2-(2-pyridylethyl)amine using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Steps E and F, mp 209.5-212° C: MS (FAB) 408 (M+1)⁺.

- 76 -

EXAMPLE XXXIV

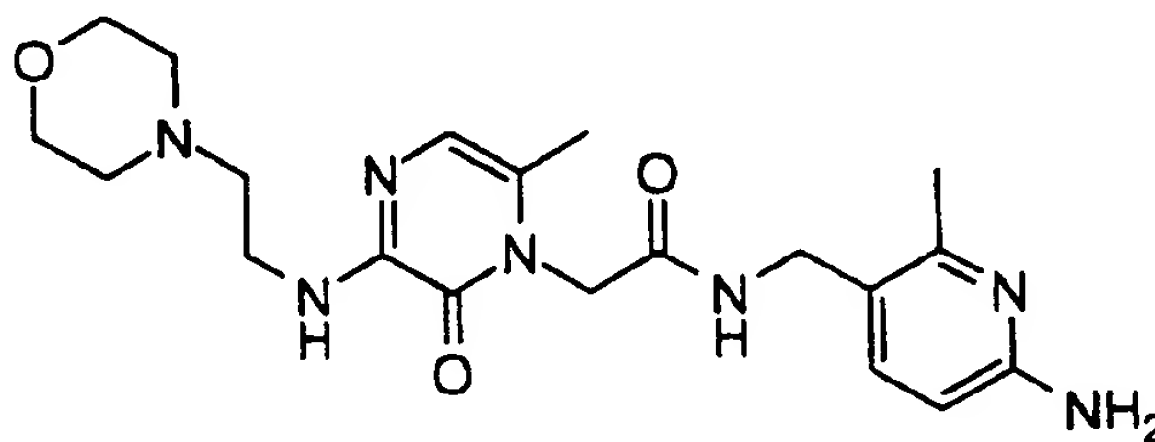
Preparation of 3-(1-Pentylamino)-5-chloro-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



The title compound was prepared from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and pentylamine using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Step F: MS (FAB) 407 (M+1)⁺.

EXAMPLE XXXV

Preparation of 3-[2-(4-Morpholino)ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



The title compound was prepared as the HCl salt from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and 2-(4-morpholinoethyl)amine using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Step E and the procedure of

METHOD 4:

Analysis for C₂₀H₂₉N₇O₃ · 3.7HCl · 3.05 H₂O

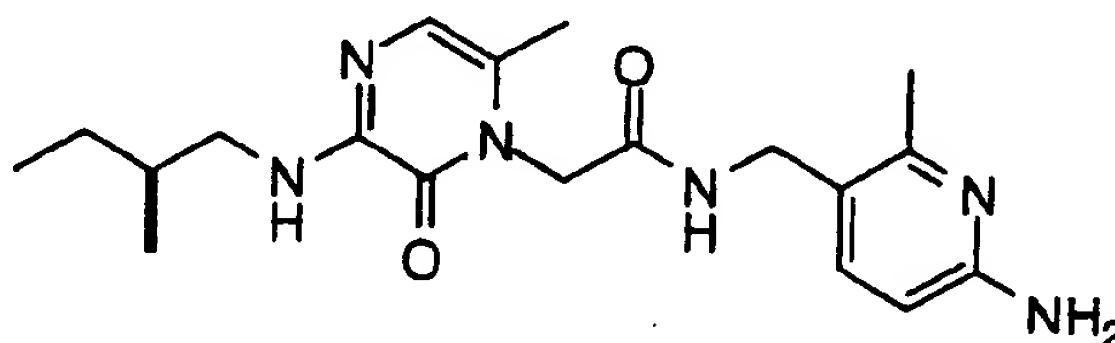
calc. C 39.69 H 6.46 N 16.20

found C 39.69 H 6.46 N 15.95

- 77 -

EXAMPLE XXXVI

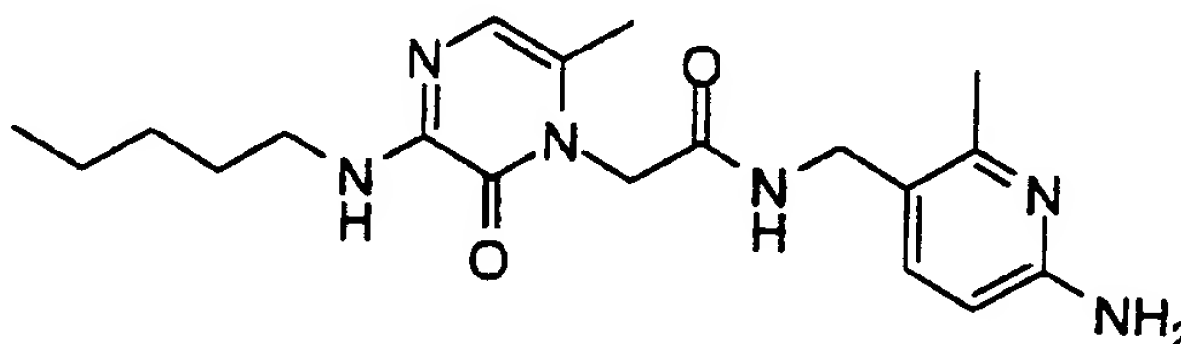
Preparation of 3-[2(S)-Methyl-1-butylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



The title compound was prepared from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and 2(S)-Methyl-1-butylamine using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Steps E and F, mp 188.5-193.5°C.

EXAMPLE XXXVII

Preparation of 3-(1-Pentylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

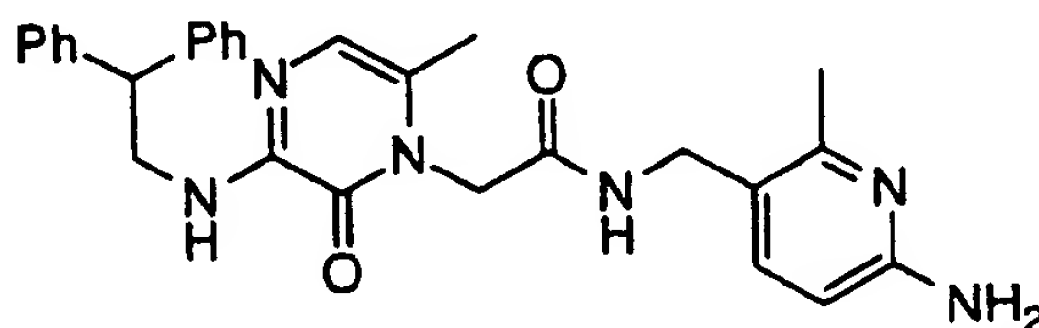


The title compound was prepared from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and 1-pentylamine using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Steps E and F, mp 115-118°C.

- 78 -

EXAMPLE XXXVIII

Preparation of 3-(2,2-Diphenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



5

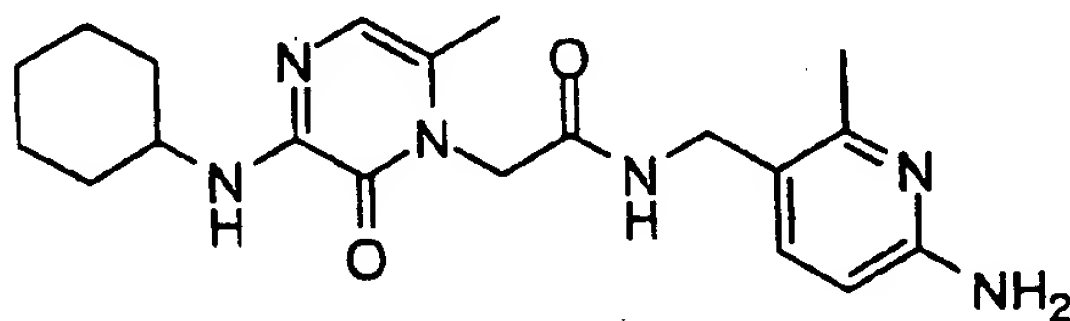
The title compound was prepared as the HCl salt from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and 2,2-diphenethylamine using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Step E and the procedure of METHOD 4:

10 Analysis for $C_{28}H_{30}N_6O_2 \cdot 2.0HCl \cdot 0.50H_2O$
calc. C 59.56 H 5.89 N 14.89
found C 59.53 H 5.72 N 14.59

EXAMPLE XXXIX

15

Preparation of 3-Cyclohexylamino-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



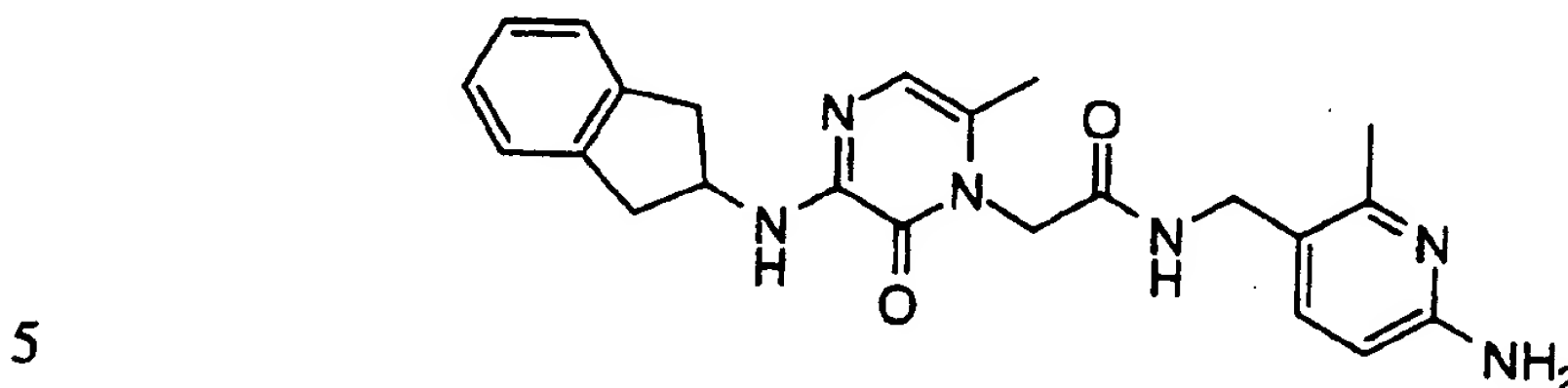
20

The title compound was prepared as the HCl salt from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and cyclohexylamine using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Step E and the procedure of METHOD 4, mp 221-227°C.

- 79 -

EXAMPLE XL

Preparation of 3-(2-Indanylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



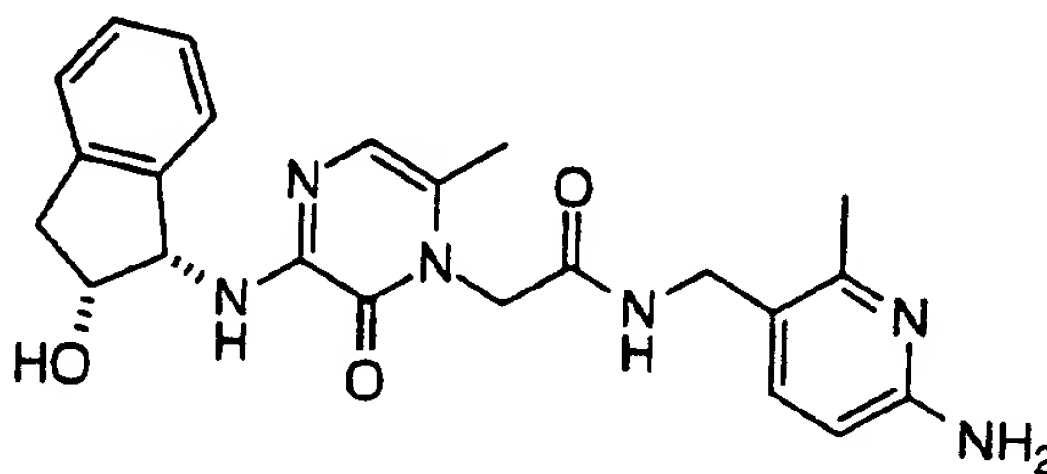
The title compound was prepared as the HCl salt from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and 2-aminoindan using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Step E and the procedure of METHOD 4:

10 Analysis for $C_{23}H_{26}N_6O_2 \cdot 2.0HCl \cdot 1.0H_2O \cdot 0.35EtOAc$
calc. C 54.25 H 6.12 N 15.56
found C 54.20 H 5.85 N 15.54

EXAMPLE XLI

15

Preparation of 3-[2(R)-Hydroxy-1(S)-indanylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

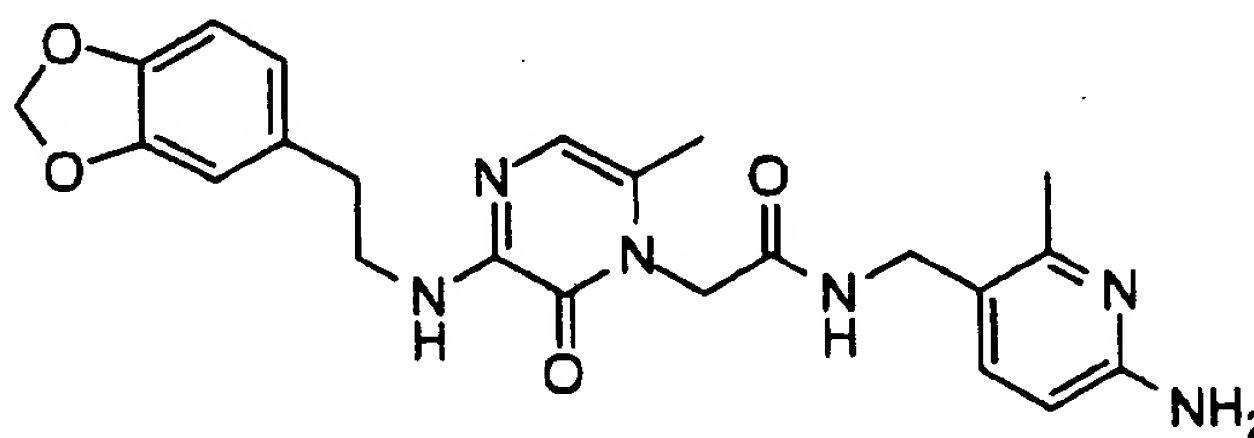


20 The title compound was prepared from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and 2(R)-hydroxy-1(S)-aminoindan using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Step E and the procedure of METHOD 4, mp 280-283°C.

- 80 -

EXAMPLE XLII

Preparation of 3-[2-(3,4-Methylenedioxyphenethylamino)]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



5

The title compound was prepared as the HCl salt from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and 2-(3,4-methylenedioxyphenyl)-ethylamine using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Step E and the procedure of METHOD 4:

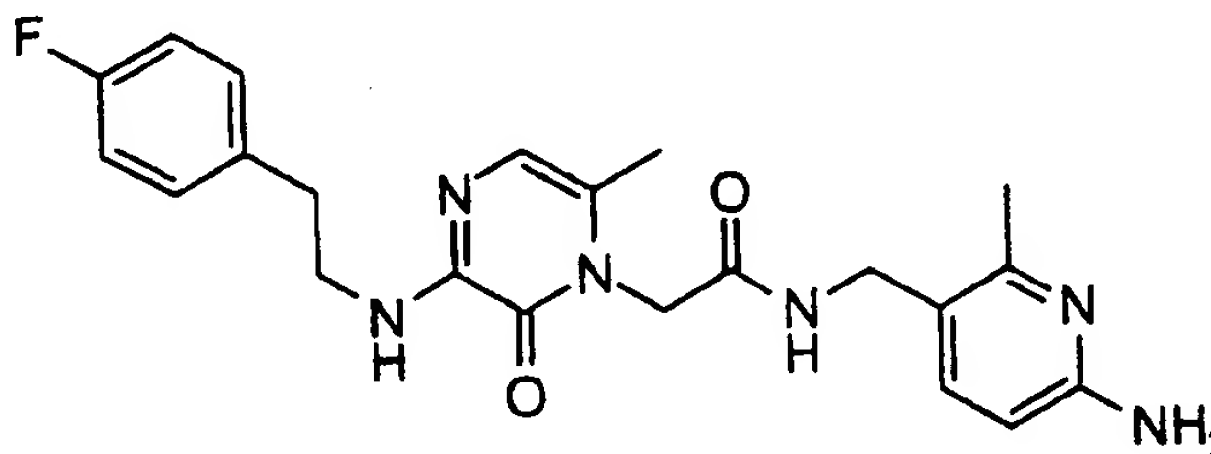
10

Analysis for $C_{23}H_{26}N_6O_4 \cdot 3.0HCl \cdot 0.30EtOAc$
calc. C 49.57 H 5.40 N 14.33
found C 49.94 H 5.25 N 14.48

15

EXAMPLE XLIII

Preparation of 3-[2-(4-Fluorophenethylamino)]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



20

The title compound was prepared as the TFA salt from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and 2-(4-fluorophenyl)-ethylamine using the procedure of EXAMPLE I, Step D, followed by the

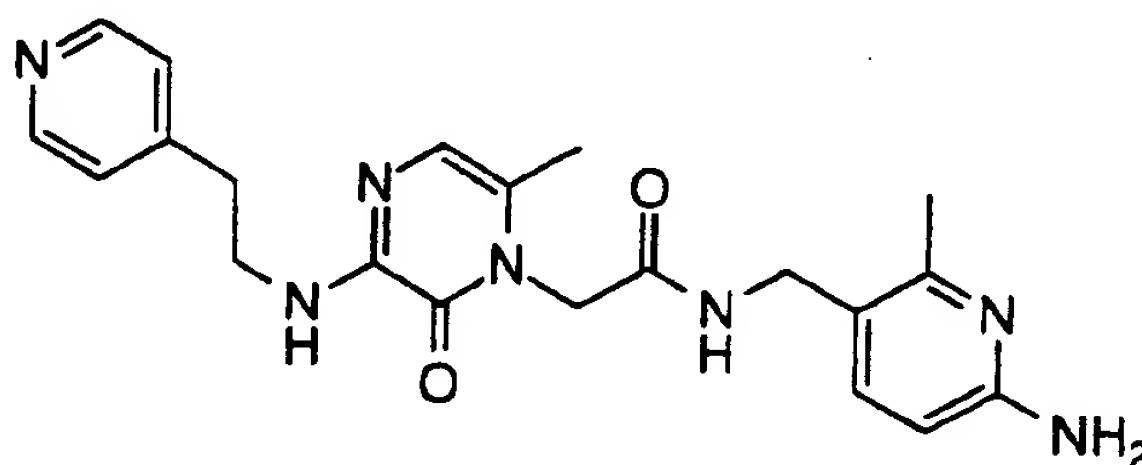
- 81 -

procedure of EXAMPLE V, Step E and the procedure of METHOD 4:
MS (FAB) 425 (M+1)⁺.

EXAMPLE XLIV

5

Preparation of 3-[2-(4-Pyridyl)-ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

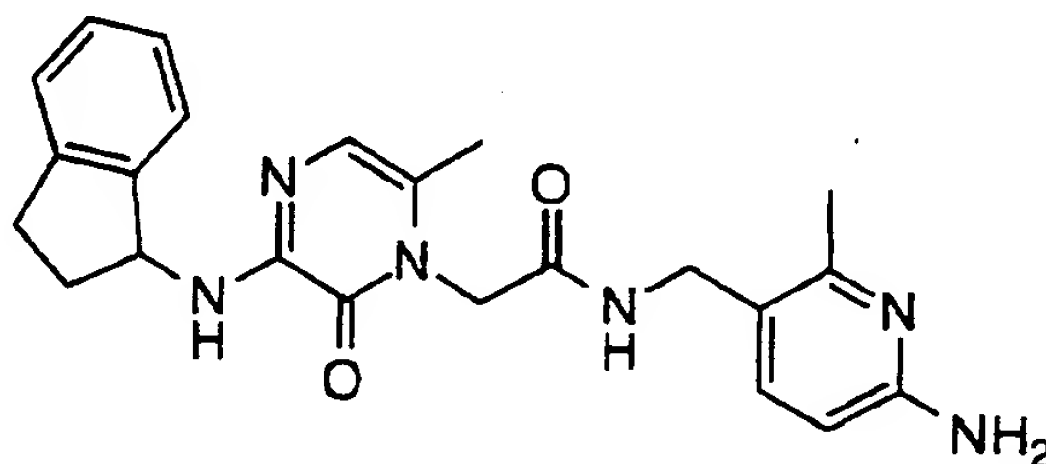


10 The title compound was prepared as the HCl salt from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and 2-(4-pyridyl)-ethylamine using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Step E and the procedure of METHOD 4, mp 220-226°C: MS (FAB) 408 (M+1)⁺.

15

EXAMPLE XLV

Preparation of rac 3-(1-Indanylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



20

The title compound was prepared as the HCl salt from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and rac 1-aminoindan

- 82 -

using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Step E and the procedure of METHOD 4:

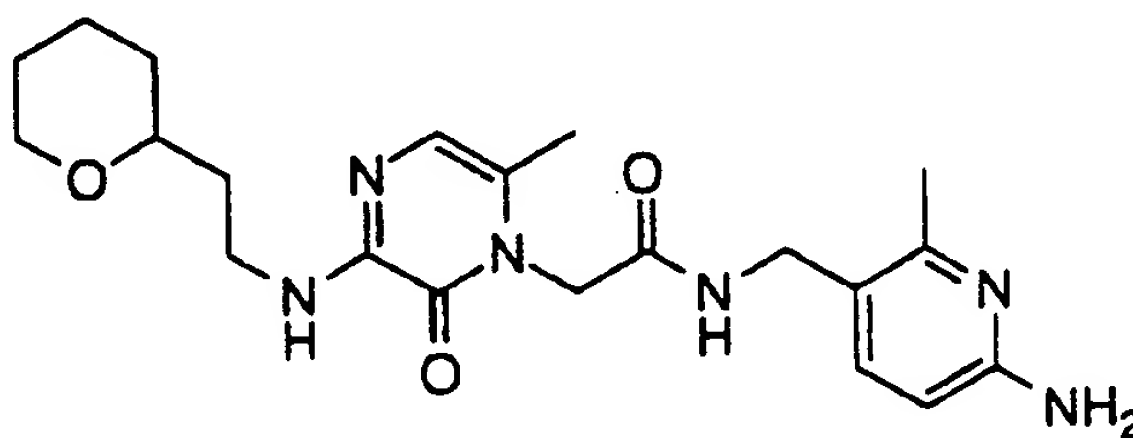
Analysis for $C_{23}H_{26}N_6O_2 \cdot 2.0HCl \cdot 1.0H_2O$

calc. C 54.22 H 5.94 N 16.50

5 found C 54.12 H 5.65 N 16.45

EXAMPLE XLVI

10 Preparation of rac 3-[2-(2-Tetrahydropyranyl)-ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



Step A: rac 2-Cyanomethylpyran

15 A mixture of rac 2-bromomethylpyran (3.0 g, 16 mmol) and sodium cyanide (1.6 g, 33 mmol) in DMF (50 ml) was heated at 100°C overnight. The solvent was then removed *in vacuo* and the residue partitioned between methylene chloride and water. The organic phase was dried over sodium sulfate. Removal of the solvent and chromatography of the residue (4:1 hexane / ethyl acetate) gave the title compound:
20 1H NMR ($CDCl_3$) δ 1.35-1.91 (m, 6 H), 2.50 (d, $J = 6.0$ Hz, 2 H), 3.59 (m, 2 H), 4.01 (m, 1 H).

Step B: rac 2-Aminoethylpyran

25 A mixture of rac 2-cyanomethylpyran (4.2 g) and 10% Pd/C (4.0 g) in 1:1 ethanol:acetic acid (150 ml) was hydrogenated at 55 psi overnight. The reaction mixture was filtered through Celite and the solvents were then removed *in vacuo*. The residue was partitioned

- 83 -

between chloroform and 10% sodium carbonate solution. The organic phase was dried over sodium sulfate. Removal of the solvent gave the title compound:

¹H NMR (CDCl₃) δ 1.32-1.84 (m, 6 H), 3.06 (m, 2 H), 3.44 (m, 2 H),
5 3.98 (m, 1 H).

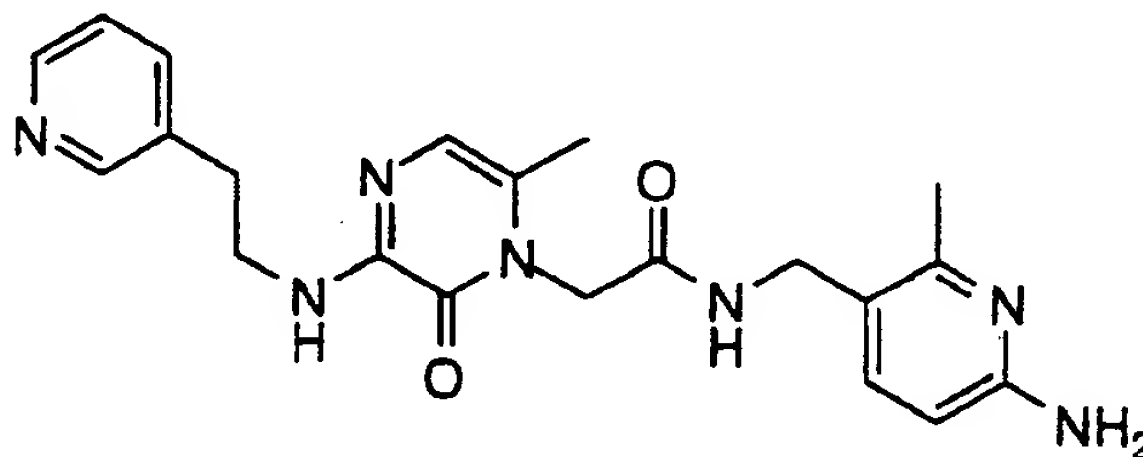
Step C: rac 3-[2-(2-Tetrahydropyranyl)-ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

10 The title compound was prepared as the TFA salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-(2-tetrahydropyranyl)-ethylamine using the procedure of EXAMPLE V, Steps C-E, followed by the procedure of METHOD 4: MS (FAB) 415 (M+1)⁺.

15

EXAMPLE XLVII

Preparation of 3-[2-(3-Pyridyl)-ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



20

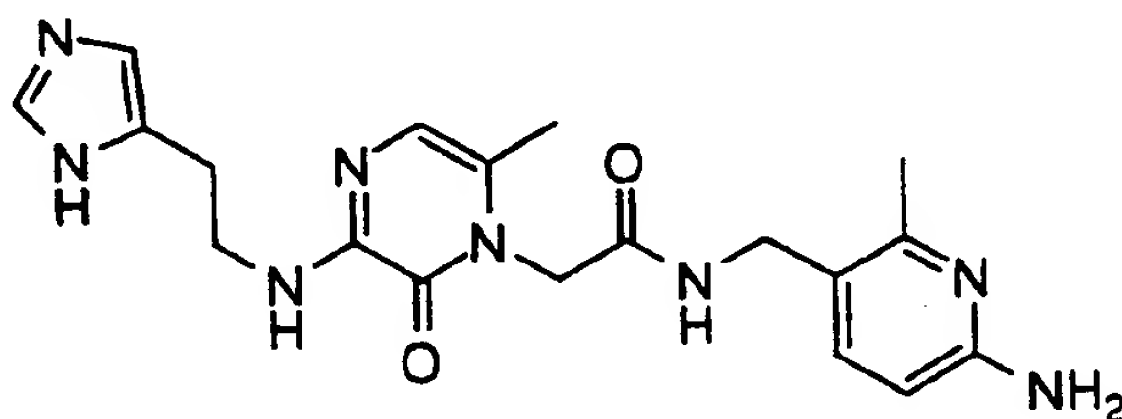
The title compound was prepared as the HCl salt from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and 2-(3-pyridyl)-ethylamine using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Step E and the procedure of METHOD 4,

25 mp >250° C: MS (FAB) 408 (M+1)⁺.

- 84 -

EXAMPLE XLVIII

Preparation of 3-[2-(4-Imidazolyl)-ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



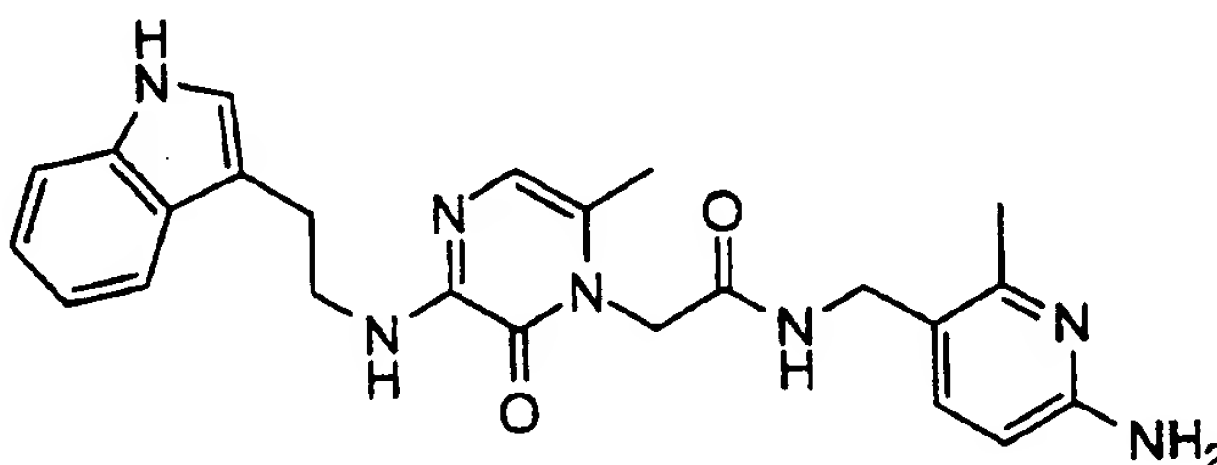
5

The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and histamine using the procedure of EXAMPLE V, Steps C-E and the procedure of METHOD 4: MS (FAB) 397 (M+1)⁺.

10

EXAMPLE IL

Preparation of 3-[2-(3-Indolyl)-ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



15

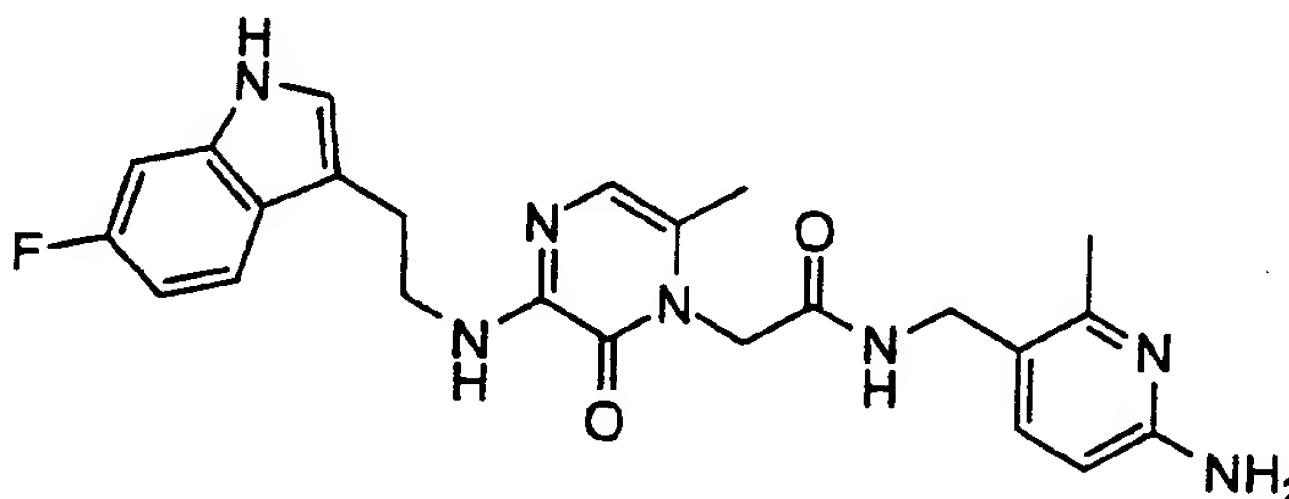
The title compound was prepared from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and tryptamine using the procedure of EXAMPLE V, Steps C-E and the procedure of METHOD 4, mp 195-197°C: MS (FAB) 446 (M+1)⁺.

20

- 85 -

EXAMPLE L

Preparation of 3-{2-[3-(6-Fluoro)-indolyl]-ethylamino}-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



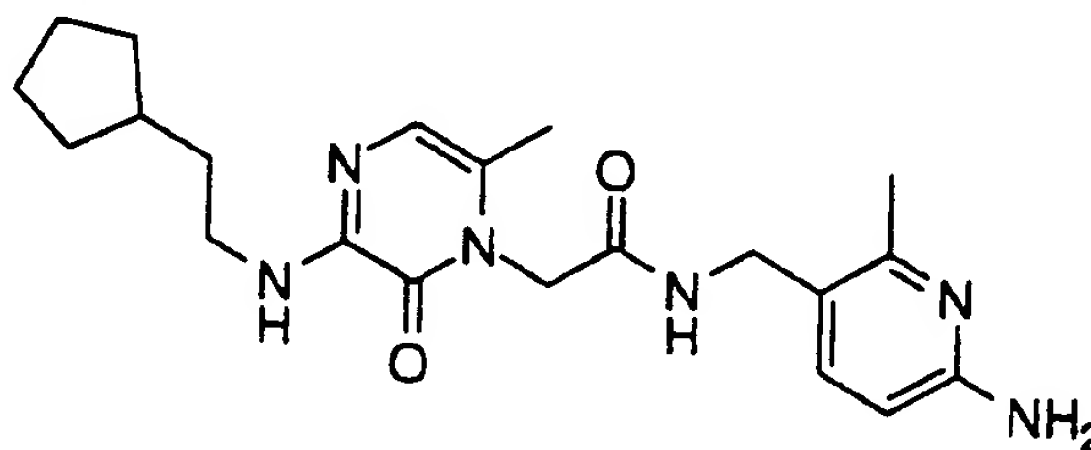
5

The title compound was prepared as the TFA salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 6-fluorotryptamine using the procedure of EXAMPLE V, Steps C-E and the procedure of METHOD 4: MS (FAB) 464 (M+1)⁺.

10

EXAMPLE LI

Preparation of 3-(2-Cyclopentylethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



15

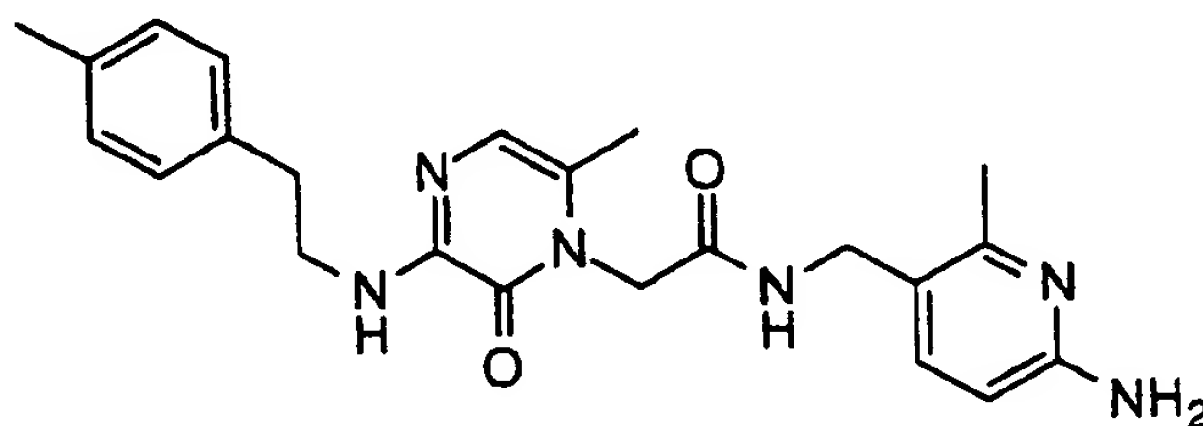
The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-cyclopentylethylamine using the procedure of EXAMPLE V, Steps C-E and the procedure of METHOD 4: MS (FAB) 399 (M+1)⁺.

20

- 86 -

EXAMPLE LII

Preparation of 3-[2-(4-methylphenyl)-ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



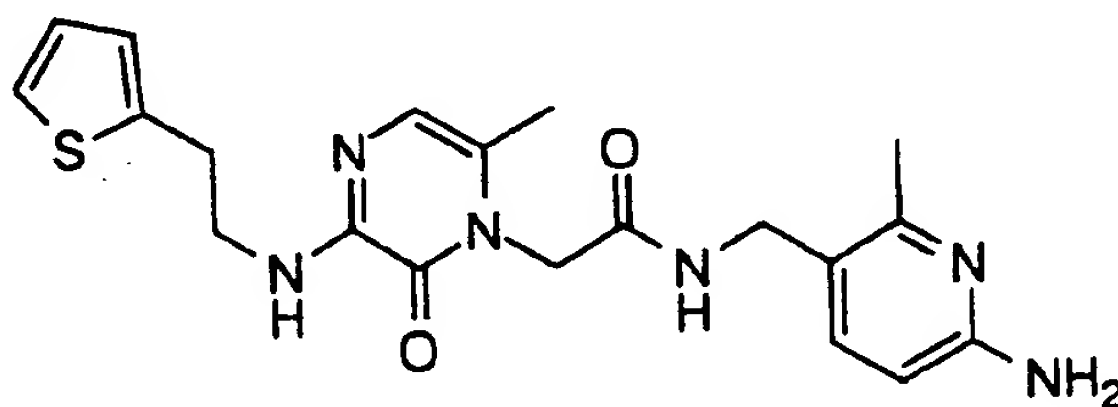
5

The title compound was prepared from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-(4-methylphenyl)ethylamine using the procedure of EXAMPLE V, Steps C-F, mp 254.5-260° C: MS (FAB) 421 (M+1)⁺.

10

EXAMPLE LIII

Preparation of 3-[2-(2-thienyl)-ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



15

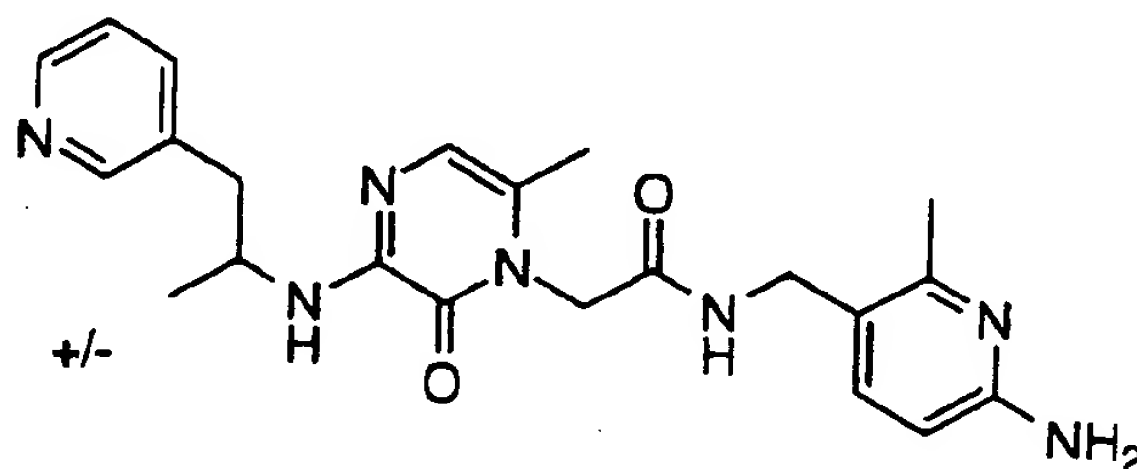
The title compound was prepared from 3,5-dichloro-6-methyl-1-carboxymethylpyrazinone and 2-(2-thienyl)ethylamine using the procedure of EXAMPLE I, Step D, followed by the procedure of EXAMPLE V, Step E and the procedure of METHOD 4, mp 245.5-

20 249.5° C: MS (FAB) 413 (M+1)⁺.

- 87 -

EXAMPLE LIV

Preparation of rac 3-[1-(3-pyridyl)-2-propylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 1-(3-pyridyl)-2-propylamine (which was prepared following the procedure of Burger et al.; *J. Org. Chem.* 1957, 22, 143) using the procedure of EXAMPLE V, Steps C-E followed by the procedure of METHOD 4: MS (FAB) 422 (M+1)⁺;

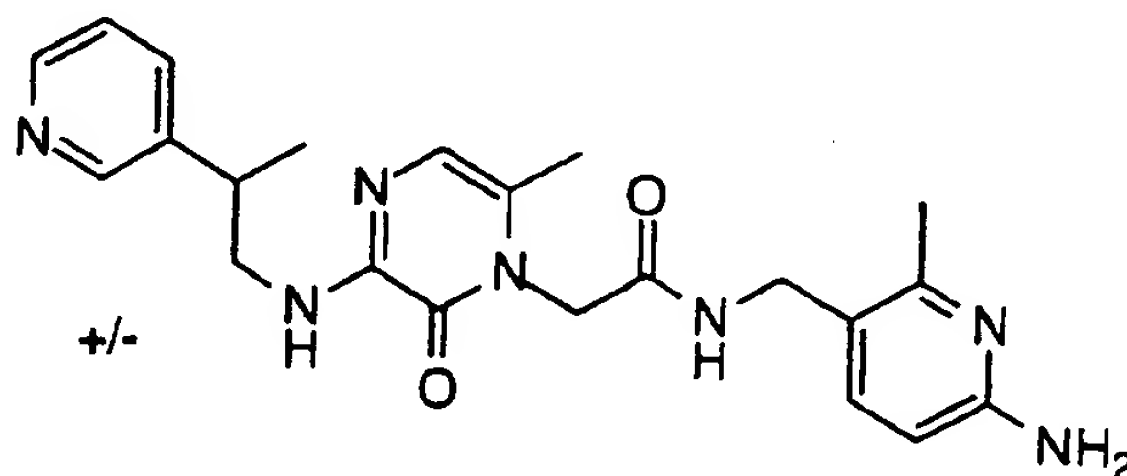
Analysis for C₂₂H₂₇N₇O₂ · 4.1HCl · 1.0 EtOAc

calc. C 47.38 H 5.98 N 14.88

15 found C 47.37 H 6.11 N 14.88

EXAMPLE LV

20 Preparation of rac 3-[2-(3-pyridyl)-1-propylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



- 88 -

Step A: 2-(3-Pyridyl)-1-nitropropane

To a solution of anhydrous CeCl_3 (8.63 g, 35.0 mmol) in 200 mL of anhydrous THF, cooled to 0°C was added MeMgBr (1.0M in ether, 11.7 mL, 35.0 mmol) dropwise. After stirring for 1.5 h the solution
5 was cooled to -40°C and a solution of 3-(2-nitroethenyl)pyridine (available from TCI-USA) (1.50 g, 10.0 mmol) in 5 mL of THF was added dropwise over 15 minutes. After 5 min the reaction was quenched with glacial AcOH (1 mL) and concentrated *in vacuo*. The residue was dissolved in methylene chloride (200 mL) and washed with NaOH (1 x
10 50 mL, 1N) and water (1 x 50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*, the residue was purified by flash column chromatography (30 x 150 mm column of SiO_2 , $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ (1:3)) to give the title compound as an oil:
 ^1H NMR (400 MHz, CDCl_3) δ 1.40 (d, $J = 6.9$ Hz, 3H), 3.62-3.71 (m, 1H), 4.53-4.62 (m, 2H), 7.26-7.36 (m, 1H), 7.54-7.59 (m, 1H), 8.48-8.53 (m, 2H).

Step B: 2-(3-Pyridyl)-1-propylamine

To a solution of 2-(3-pyridyl)-1-nitropropane (0.91 g, 5.48
20 mmol) in 20 mL of ethanol and 0.1 mL of 12N HCl was added 10% Pd/C (1.00 g) under argon. The solution was evacuated and flushed with hydrogen several times, place under an atmosphere of hydrogen and vigorously stirred. After 14 h the mixture was evacuated and flushed with argon several times, filtered through celite and washed with 200 mL
25 of ethanol. The volatiles were removed *in vacuo* to provide a residue which was partitioned between methylene chloride (100 mL) and NaOH (50 mL, 10%) and the aqueous layer was extracted with methylene chloride (2 x 100 mL). The combined organic layers were dried over MgSO_4 , filtered, concentrated *in vacuo* and the residue was purified by
30 flash column chromatography (20 x 150 mm column of SiO_2 , $\text{CH}_2\text{Cl}_2/\text{CH}_2\text{Cl}_2$ saturated with NH_3/MeOH 60:39:1) to give the title compound as an oil:

- 89 -

¹H NMR (400 MHz, CDCl₃) δ 1.28 (d, J = 6.8 Hz, 3H), 2.74-2.85 (m, 1H), 2.87-2.92 (m, 2H), 7.23-7.26 (m, 1H), 7.51-7.54 (m, 1H), 8.47-8.49 (m, 2H).

5 Step C: rac 3-[2-(3-Pyridyl)-1-propylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

The title compound was prepared from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-(3-pyridyl)-1-propylamine using the procedure of EXAMPLE V, Steps C-F:

10 Analysis for C₂₂H₂₇N₇O₂ · 0.1 H₂O

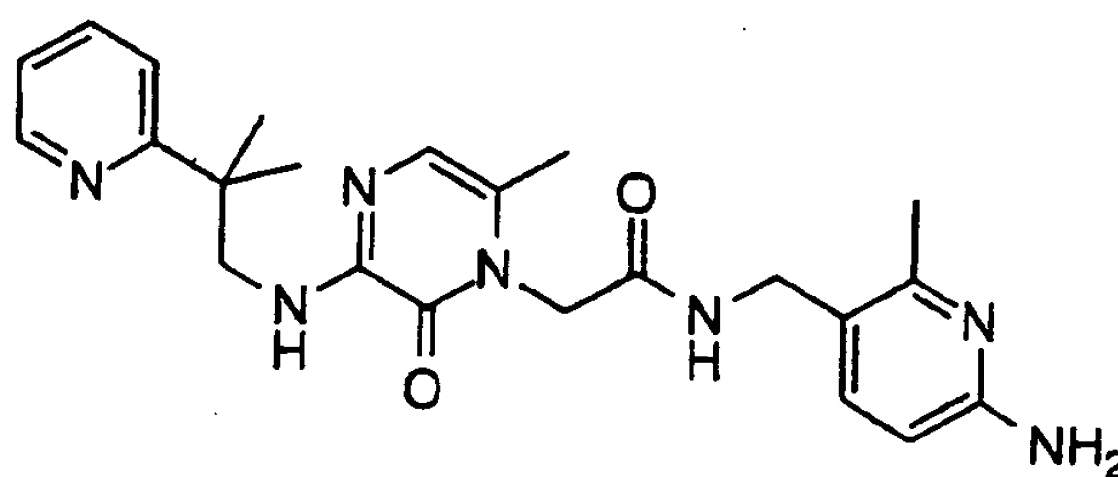
calc. C 62.42 H 6.48 N 23.10

found C 62.08 H 6.28 N 23.55

EXAMPLE LVI

15

Preparation of 3-[2-Methyl-2-(2-pyridyl)-1-propylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



20 Step A: 2-Methyl-2-(2-pyridyl)-propionitrile

To a solution of 2-pyridylacetonitrile (1.00g, 8.44 mmol) in anhydrous DMF (20 mL) cooled to 0°C was added NaH (0.743g, 18.58 mmol, 60% by wt dispersion in mineral oil) portionwise. After 10 minutes, iodomethane (1.31 mL, 21.11 mmol) was added via syringe over a 15 minute period. After 1 h the reaction was diluted into ethyl acetate (200 mL) and washed with water (5 x 20 mL) and brine (1 x 20 mL) and dried over MgSO₄. The solution was filtered, the volatiles were removed *in vacuo* and the oil was purified by flash column chromatography (30 x

- 90 -

150 mm column of SiO₂, EtOAc/Hex gradient elution 1:4 to 1:3) to give the title compound as a colorless oil:

¹H NMR (400 MHz, CDCl₃) δ 1.77 (s, 6H), 7.22-7.27 (m, 1H), 7.59 (dd, J = 7.8 and 0.9 Hz, 1H), 7.71-7.75 (m, 1H), 8.59-8.61 (m, 1H).

5

Step B: 2-Methyl-2-(2-pyridyl)-1-propylamine

To a solution of 2-methyl-2-(2-pyridyl)-propionitrile (1.018 g, 6.97 mmol) in 25 mL of anhydrous diethyl ether under a blanket of Argon was added LiAlH₄ (0.538 g, 14.17 mmol) portionwise. After 1 h the reaction was quenched with the addition of water (1 mL), NaOH (1.0 mL, 1N), water (8 mL) then diethyl ether (20 mL) and let stir for 10 h. The solution was filtered through a plug of celite and washed with diethyl ether:MeOH (1:1) (200 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (30 x 150 mm column of SiO₂, CH₂Cl₂/CH₂Cl₂ saturated with NH₃/MeOH gradient elution 60:39:1 to 60:38:2 to 60:37:3) to give the title compound as a resin:

¹H NMR (400 MHz, CDCl₃) δ 1.21 (br s, 2H), 1.38 (s, 6H), 2.98 (s, 2H), 7.05-7.14 (m, 1H), 7.34-7.38 (m, 1H), 7.60-7.64 (m, 1H), 8.59-8.61 (m, 1H).

20

Step C: 3-(2-methyl-2-(2-pyridyl)-1-propylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-methyl-2-(2-pyridyl)-1-propylamine using the procedure of EXAMPLE V, Steps C-E followed by the procedure of METHOD 4: MS (FAB) 436 (M+1)⁺;

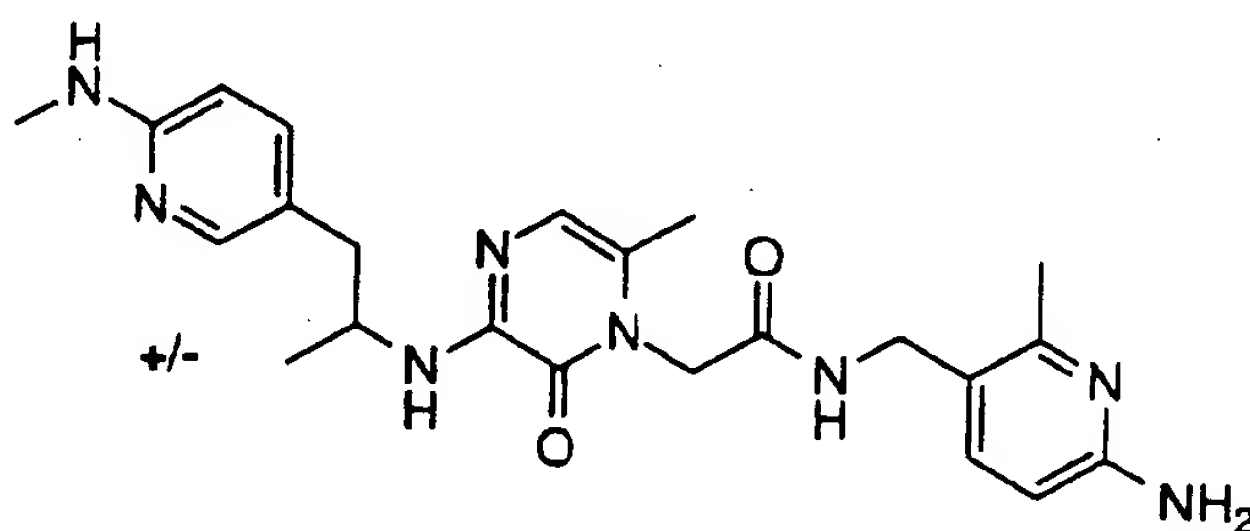
Analysis for C₂₃H₂₉N₇O₂ · 3.0 HCl · 0.3 EtOAc
calc. C 50.87 H 6.07 N 17.16
found C 50.52 H 5.76 N 16.88

30

- 91 -

EXAMPLE LVII

Preparation of rac 3-{1-[5-(2-Methylaminopyridyl)]-2-propylamino}-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



Step A: Methyl-6-(t-butoxycarbonylamino)-nicotinate

To a solution of 6-aminonicotinic acid (2.00 g, 14.48 mmol) dissolved in chloroform/MeOH (90 mL : 30 mL) was added (trimethylsilyl)diazomethane (2.0M in hexanes, 25 mL). After 15 minutes acetic acid (0.1 mL) was added and the solution was concentrated *in vacuo* to a residue. Trituration with EtOAc/Hex (2:1) provided methyl-6-aminonicotinate as a pale yellow solid after filtration. This material was used directly in the next step. To a solution of methyl-6-aminonicotinate (1.86 g, 12.22 mmol) dissolved in methylene chloride (90 mL) was added di-t-butyl dicarbonate (2.69 g, 12.34 mmol), 4-dimethylaminopyridine (0.15 g, 1.22 mmol) and triethylamine (2.00 mL, 14.66 mmol). After 14 h the reaction was diluted with EtOAc (400 mL) and washed with citric acid (1 x 50 mL, 10%), water (1 x 50 mL) and brine (1 x 50 mL) and was dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (40 x 150 mm column of SiO₂, EtOAc/Hex gradient elution 1:6, 1:5, 1:3) to give the title compound as a white solid:

¹H NMR (400 MHz, CDCl₃) δ 1.56 (s, 9H), 3.91 (s, 3H), 8.06 (d, J = 8.2 Hz, 1H), 8.24-8.27 (m, 1H), 8.57 (br s, 1H), 8.93 (dd, J = 0.7 and 2.4 Hz, 1H).

- 92 -

Step B: 2-(t-Butoxycarbonylamino)-5-pyridinecarboxaldehyde

- To a solution of methyl-6-(tert-butoxycarbonylamino)-nicotinate (2.20 g, 8.72 mmol) in anhydrous THF (50 mL), cooled to -30°C was added DIBAL-H (1.0M in hexane, 34.8 mL, 34.8 mmol) dropwise. After 1 h, 40 mL of a saturated solution of Rochelle salts was added and stirred vigorously for 10 h. The volatiles were removed *in vacuo* and the aqueous layer was extracted with methylene chloride (3 x 50 mL). The organic layer was washed with water (1 x 50 mL) and brine (1 x 50 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*.
- 10 The residue was used directly in the next step. To a solution of oxalyl chloride (4.12 g, 32.46 mmol) in methylene chloride (30 mL), cooled to -78°C, was added DMSO (2.54 g, 32.46 mmol) dissolved in methylene chloride (9 mL) dropwise. After 20 minutes, the crude alcohol (1.82 g, 8.11 mmol) dissolved in 35 mL of methylene chloride was added
- 15 followed by triethylamine (4.92 g, 48.66 mmol). The ice bath was removed and the reaction stirred for 1 hr at rt, then water (30 mL) was added. The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 50 mL). The organic layer was washed with water (1 x 50 mL) and brine (1 x 50 mL), dried over MgSO₄, filtered,
- 20 and concentrated *in vacuo*. The residue was purified by flash column chromatography (30 x 150 mm column of SiO₂, EtOAc/methylene chloride 1:11) to give the title compound as a colorless solid:
- ¹H NMR (400 MHz, CDCl₃) δ 1.55 (s, 9H), 7.79 (br s, 1H), 8.13-8.14 (m, 2H), 8.71 (dd, J = 1.1 and 1.8 Hz, 1H), 9.96 (s, 1H).

25

Step C: 2-(t-Butoxycarbonylamino)-5-[1-(2-nitropropenyl)]-pyridine

- To a solution of 2-(t-butoxycarbonylamino)-5-pyridinecarboxaldehyde (1.20 g, 5.40 mmol) dissolved in N-methylmorpholine (40 mL) was added nitroethane (2.20 g, 27.0 mmol), potassium fluoride (0.144 g, 2.49 mmol), and 18-crown-6 (0.036g).
- 30 Acetic anhydride (2.20 g, 21.6 mmol) and a catalytic amount of 4-dimethylaminopyridine (0.05g) was added after 1 hr. The reaction was quenched after 12h by pouring into 200 mL of ice. The aqueous layer was extracted with methylene chloride (3 x 75 mL) and the combined

- 93 -

organic layer was washed with water (2 x 50 mL) and brine (1 x 50 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was triturated with methylene chloride and the solid was collected by filtration to give the title compound as a pale yellow solid:

- 5 ¹H NMR (400 MHz, CDCl₃) δ 1.54 (s, 9H), 2.47 (d, J = 0.9 Hz, 3H), 7.41 (br s, 1H), 7.76 (dd, J = 2.3 and 8.8 Hz, 1H), 8.04 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 8.33 (d, J = 2.4 Hz, 1H).

Step D: rac 1-[5-(2-Methylaminopyridyl)]-2-propylamine

- 10 To a solution of 2-(t-butoxycarbonylamino)-5-[1-(2-nitropropenyl)]-pyridine (0.20 g, 0.716 mmol) dissolved in THF (8 mL), cooled to 0°C, was added borane THF complex (4.30 mL, 1.0 M in THF, 4.30 mmol). The ice bath was removed and NaBH₄ (0.0135 g, 0.358 mmol) was added and the reaction was warmed to 65°C. After 24 h the
15 reaction was poured into ice (50 mL), acidified to pH 2 with 3 N HCl and warmed to 65°C for 2 h. The pH was adjusted to 8 with aqueous NaOH (1N) and the solvent was removed *in vacuo*. The aqueous layer was extracted with methylene chloride (3 x 75 mL) and the combined organic layers were washed with water (2 x 50 mL) and brine (1 x 50 mL), dried
20 over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (15 x 150 mm column of SiO₂, CH₂Cl₂/CH₂Cl₂ saturated with NH₃/MeOH 60:37:3) to give the title compound an oil:

- 25 ¹H NMR (400 MHz, CDCl₃) δ 1.09 (d, J = 6.2 Hz, 3H), 2.37-2.42 (m, 1H), 2.54 (dd, J = 5.5 and 13.7 Hz, 1H), 2.90 (d, J = 4.9 Hz, 3H), 3.03-3.09 (m, 1H), 4.62 (br s, 1H), 6.34-6.37 (m, 1H), 7.26-7.33 (m, 1H), 7.89-7.92 (m, 1H).

Step E: rac 3-{1-[5-(2-Methylaminopyridyl)]-2-propylamino}-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

- 30 The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and rac 1-[5-

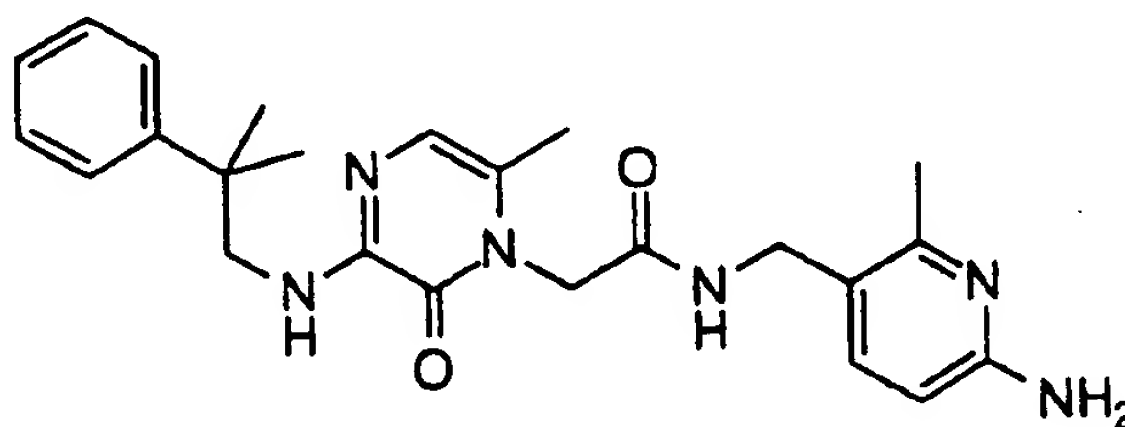
- 94 -

(2-methylaminopyridyl)]-2-propylamine using the procedure of
EXAMPLE V, Steps C-F: MS (FAB) 451 (M+1)⁺;
Analysis for C₂₃H₃₀N₈O₂ · 2.45 HCl · 1.25 CH₂Cl₂
calc. C 45.08 H 5.45 N 17.35

5 found C 45.03 H 5.48 N 17.37.

EXAMPLE LVIII

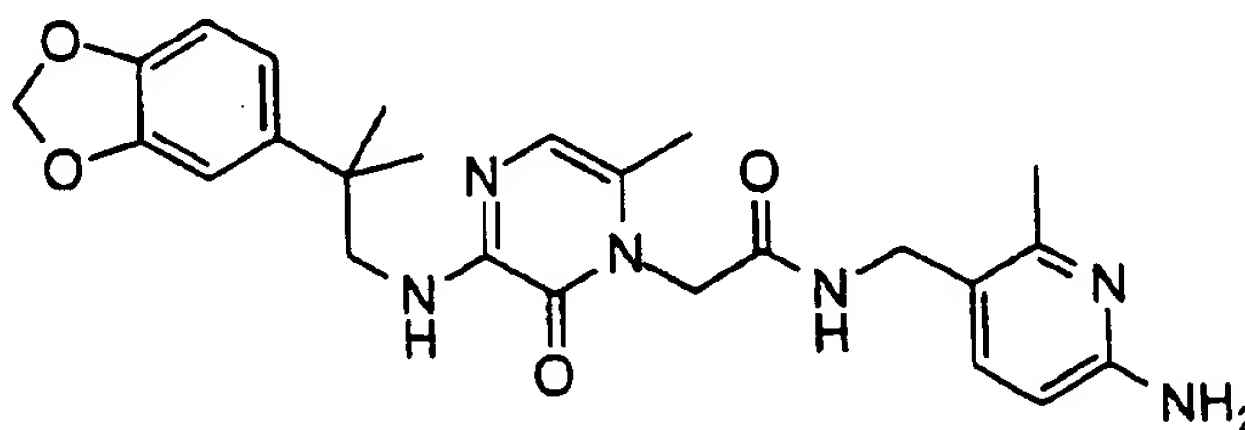
10 Preparation of 3-(2-Methyl-2-phenyl-1-propylamino)-6-methyl-1-(2-
amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



The title compound was prepared from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-methyl-2-phenyl-1-propylamine using the procedure of EXAMPLE V,
15 Steps C-F, mp 179-181° C: MS (FAB) 435 (M+1)⁺.

EXAMPLE LIX

20 Preparation of 3-[2-Methyl-2-(3,4-methylenedioxyphenyl)-1-propylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

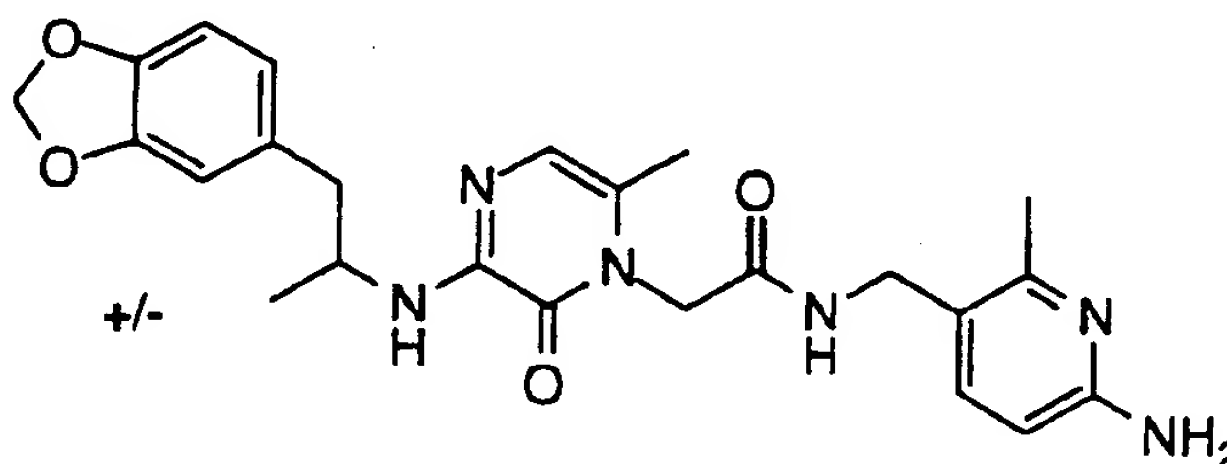


- 95 -

The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-methyl-2-(3,4-methylenedioxyphenyl)-1-propylamine (which was prepared from 3,4-methylenedioxyphenylacetonitrile using the procedure of EXAMPLE LVI, Steps A and B) using the procedure of EXAMPLE V, Steps C-F: MS (FAB) 479 (M+1)⁺;
 Analysis for C₂₅H₃₀N₆O₄ · 2.10 HCl · 0.7 H₂O
 calc. C 52.88 H 5.95 N 14.80
 found C 52.88 H 5.96 N 14.51.

EXAMPLE LX

Preparation of rac 3-[1-(3,4-methylenedioxyphenyl)-2-propylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



Step A: rac 1-(3,4-methylenedioxyphenyl)-2-propylamine

To a solution of 1-(3,4-methylene dioxyphenyl)-2-nitropropene (0.938 g, 4.53 mmol) dissolved in absolute ethanol (40 mL), methanol (8 mL), and HCl (4N, 4 mL) under an atmosphere of argon was added Pd/C (10%, 0.902g). The mixture was placed under a hydrogen atmosphere (balloon, 1 atm) and stirred for 14 h. The reaction was filtered through celite, washing with ethanol (200 mL), and concentrated *in vacuo* to give the title compound as a pale brown solid:
¹H NMR (400 MHz, CDCl₃) δ 1.35 (d, J = 6.6 Hz, 3H), 2.76 (dd, J = 8.6 and 13.5 Hz, 1H), 3.09 (dd, J = 5.9 and 13.5 Hz, 1H), 3.41-3.49 (m, 1H), 5.94 (s, 2H), 6.27-6.77 (m, 3H).

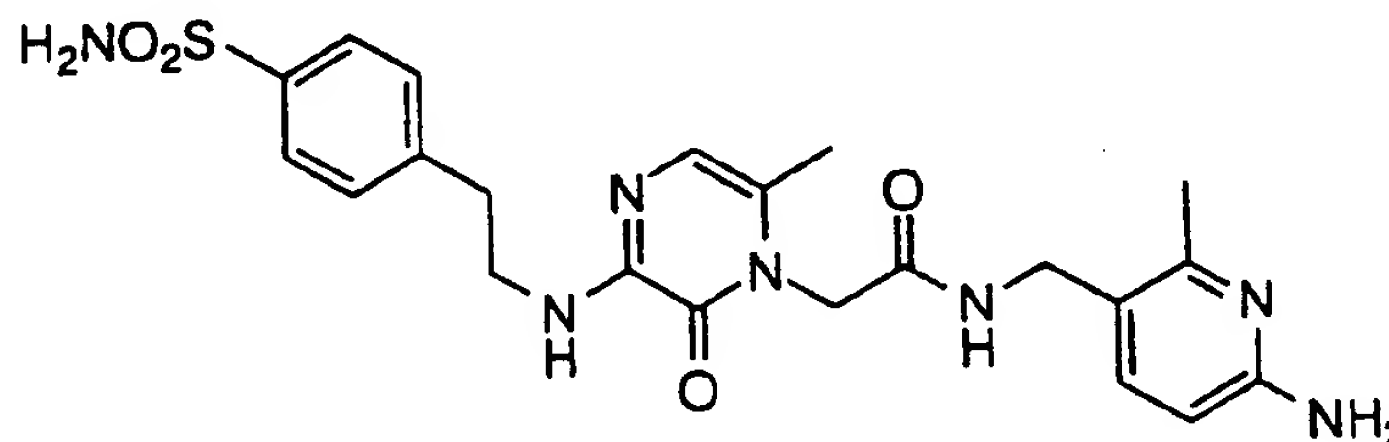
- 96 -

Step B: rac 3-[1-(3,4-methylenedioxyphenyl)-2-propylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

- The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone 1-(3,4-methylenedioxyphenyl)-2-propylamine using the procedure of EXAMPLE V, Steps C-E followed by the procedure of METHOD 4: MS (FAB) 465 (M+1)⁺;
Analysis for C₂₄H₂₈N₆O₄ · 2.40 HCl · 0.65 EtOAc
10 calc. C 52.43 H 5.89 N 13.79
found C 52.39 H 5.57 N 13.82.

EXAMPLE LXI

- 15 Preparation of 3-[2-(4-Sulfonamidophenyl)ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

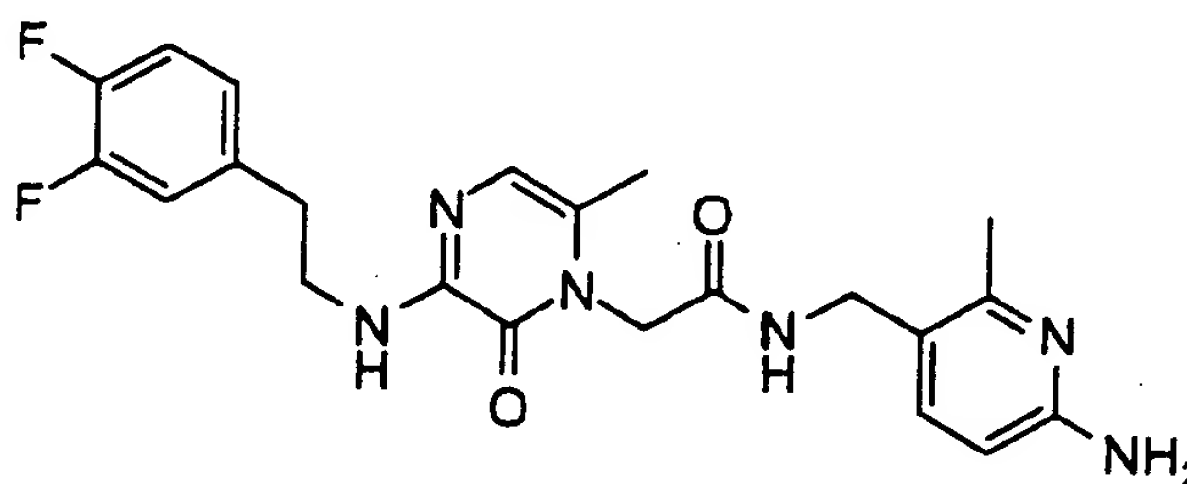


- The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 4-(2-aminoethyl)benzenesulfonamide using the procedure of EXAMPLE V, Steps C-E followed by the procedure of METHOD 4, mp 214-221°C: MS (FAB) 486 (M+1)⁺.
- 20

- 97 -

EXAMPLE LXII

Preparation of 3-[2-(3,4-Difluorophenyl)ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



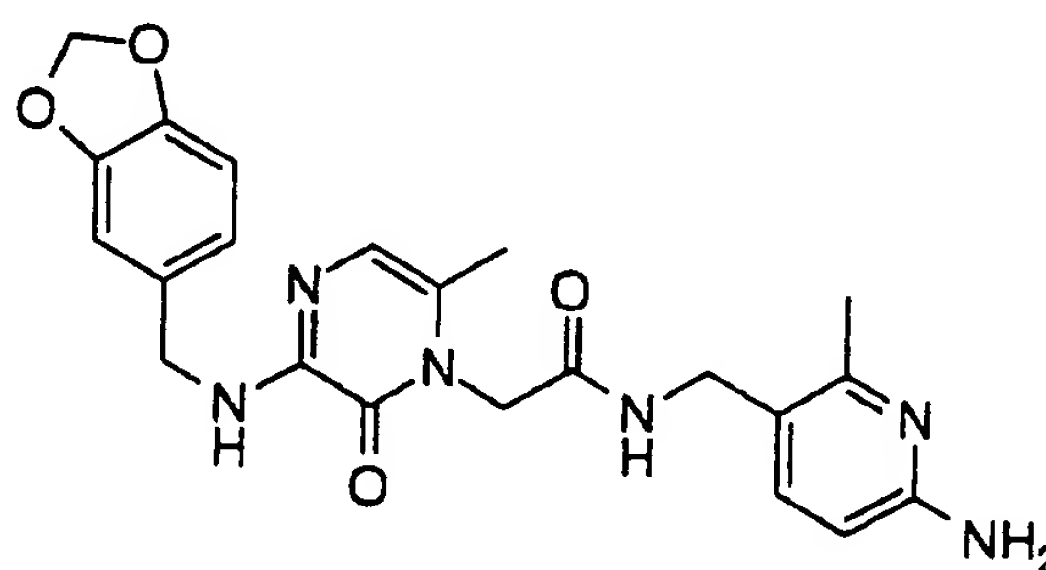
5

The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-(3,4-difluorophenyl)ethylamine using the procedure of EXAMPLE V, Steps C-E followed by the procedure of METHOD 4, mp >235° C, MS (FAB)

10 443 (M+1)⁺.EXAMPLE LXIII

Preparation of 3-(3,4-Methylenedioxybenzylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

15



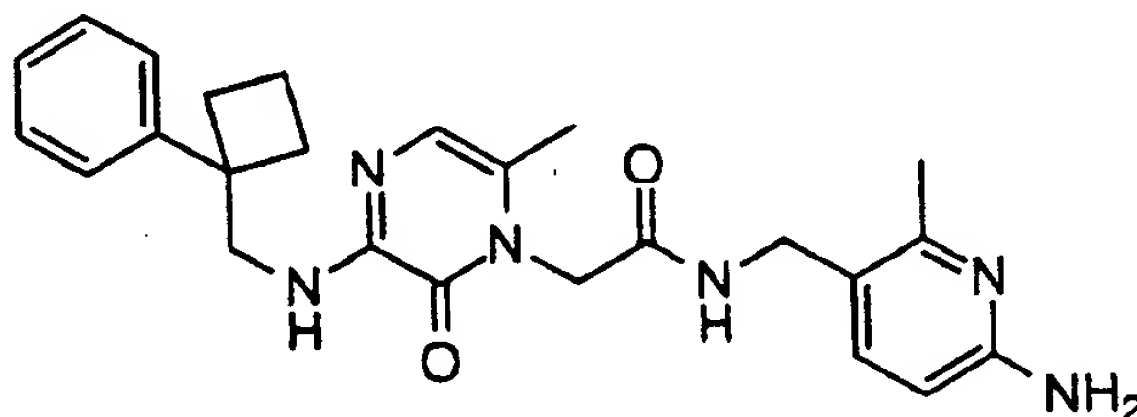
The title compound was prepared as the HCl salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 3,4-methylenedioxybenzylamine using the procedure of EXAMPLE V, Steps C-E followed by the procedure of METHOD 4, mp >255° C: MS (FAB) 437 (M+1)⁺.

20

- 98 -

EXAMPLE LXIV

Preparation of 3-(1-Phenyl-1-cyclobutanemethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



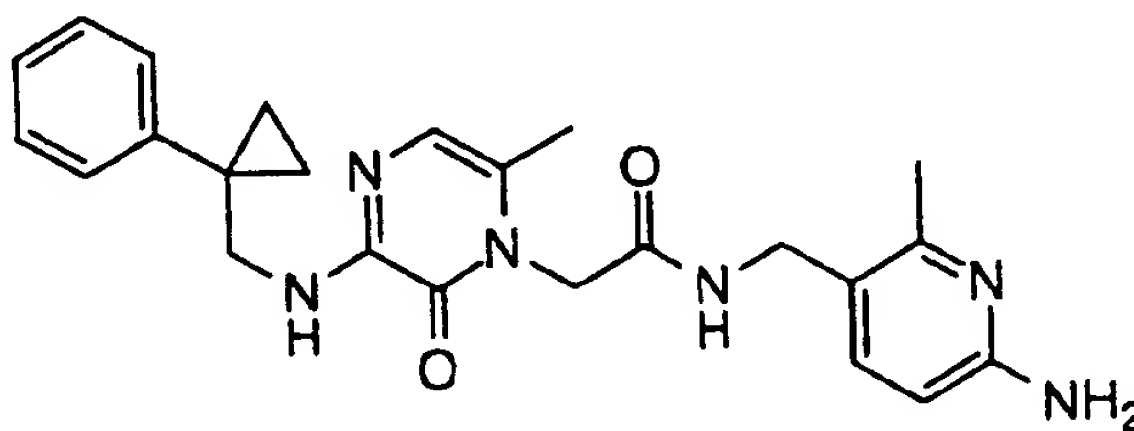
5

The title compound was prepared as the HCl salt 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 1-phenyl-1-cyclobutanemethylamine (which was prepared from 1-phenyl-1-cyclobutanecarbonitrile using the procedure of EXAMPLE LVI, Step B) using the procedure of EXAMPLE V, Steps C-E followed by the procedure of METHOD 4, mp 252-259°C: MS (FAB) 447 (M+1)⁺.

10

EXAMPLE LXV

Preparation of 3-(1-Phenyl-1-cyclopropanemethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone



20

The title compound was prepared from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 1-phenyl-1-cyclopropanemethylamine (which was prepared from 1-phenyl-1-cyclopropanecarbonitrile using the procedure of EXAMPLE LVI, Step

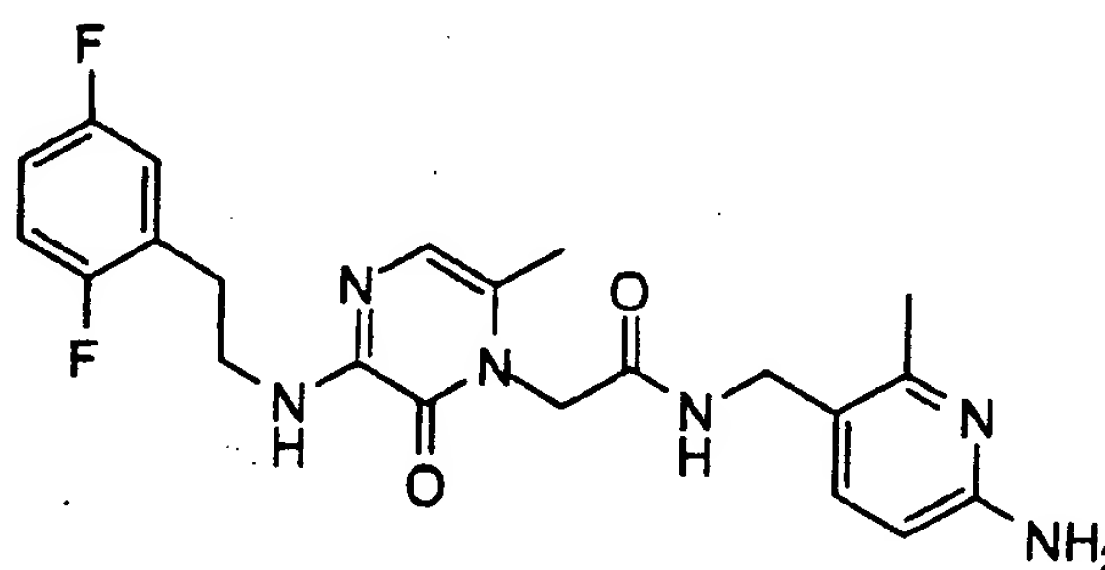
- 99 -

B) using the procedure of EXAMPLE V, Steps C-E followed by the procedure of METHOD 4: MS (FAB) 433 (M+1)⁺.

EXAMPLE LXVI

5

Preparation of 3-[2-(2,5-Difluorophenyl)ethylamino]-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone

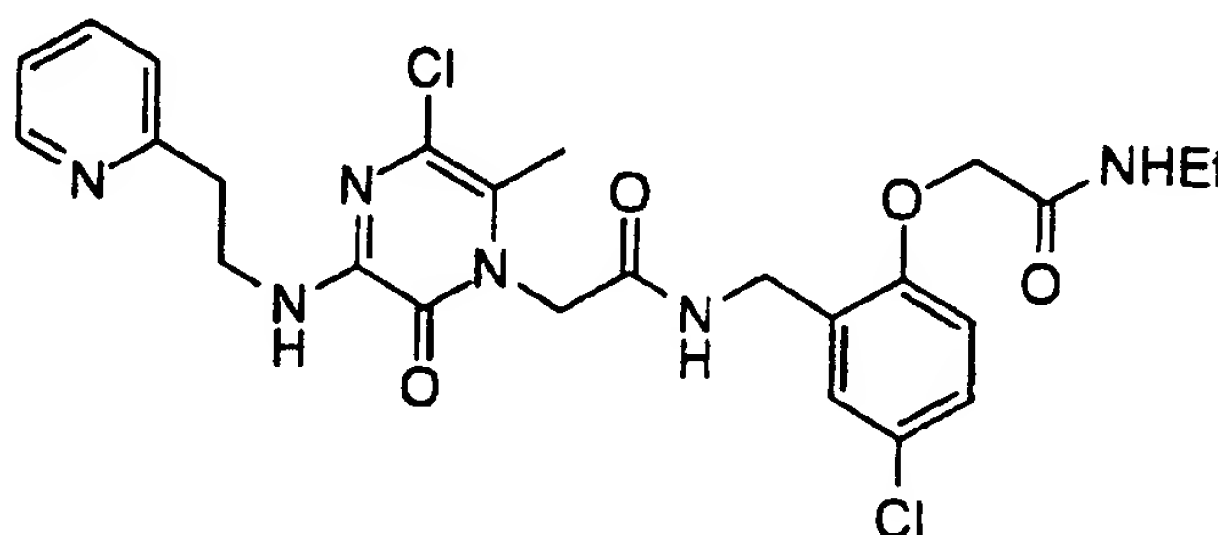


The title compound was prepared as the TFA salt from 1-benzyloxycarbonylmethyl-3,5-dichloro-6-methylpyrazinone and 2-(2,5-difluorophenyl)ethylamine using the procedure of EXAMPLE V, Steps C-F: MS (FAB) 443 (M+1)⁺.

EXAMPLE LXVII

15

3-[2-(2-Pyridyl)ethylamino]-5-chloro-6-Methyl-1-[Ethyl-(2-Methylcarboxamidomethyl-4-Chlorophenoxy)-Acetamido]-2-Pyrazinone



The title compound was prepared from 3,5-dichloro-6-methyl-1-[ethyl-(2-methyl-carboxamidomethyl-4-chlorophenoxy)-

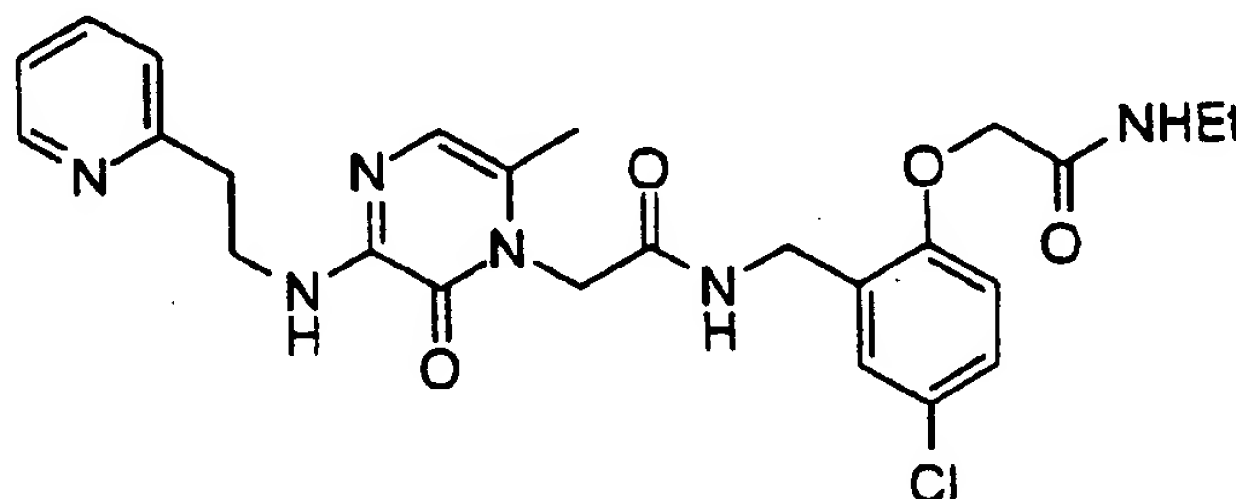
20

- 100 -

acetamido]-pyrazinone [which was prepared using the procedure of
EXAMPLE III, Step A, from 3,5-dichloro-6-methyl-1-
carboxymethylpyrazinone and ethyl-2-aminomethyl-4-chlorophenoxy)-
acetamide]] and 2-(2-pyridyl)ethylamine using the procedure of
5 EXAMPLE III, Step B, MP 207-209°C.

EXAMPLE LXVIII

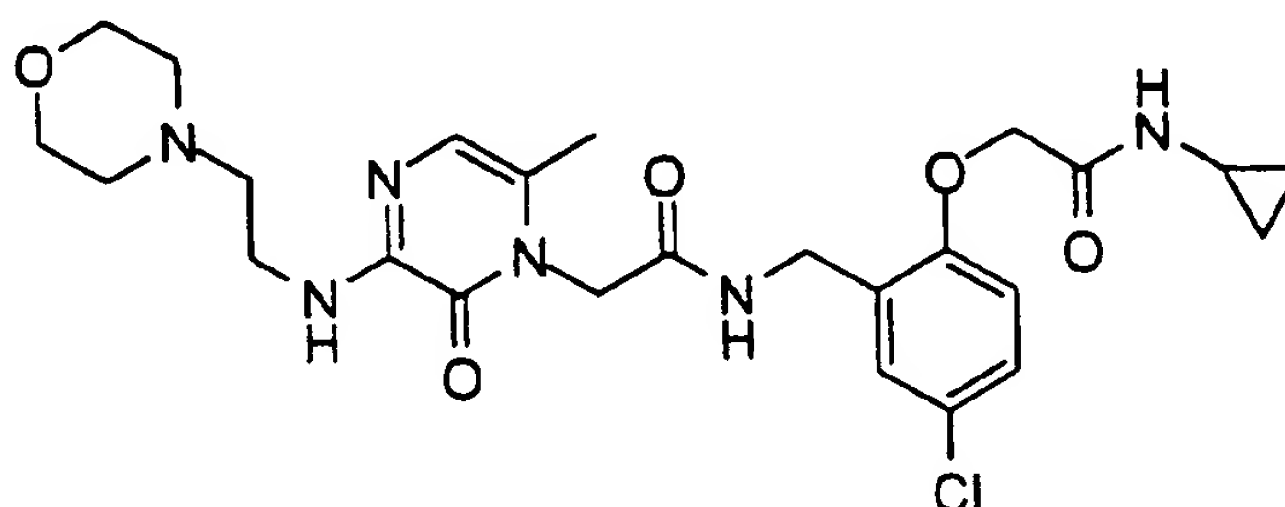
10 3-[2-(2-Pyridyl)ethylamino]-6-Methyl-1-[Ethyl-(2-
Methylcarboxamidomethyl-4-Chlorophenoxy)-Acetamido]-2-Pyrazinone



The title compound was prepared from 3-[2-(2-
pyridyl)ethylamino]-6-methyl-1-carboxymethylpyrazinone and ethyl-2-
aminomethyl-4-chlorophenoxy)-acetamide using the procedure of
15 EXAMPLE V, Step F, MP 195-197°C.

EXAMPLE LXIX

20 3-[2-(4-Morpholino)ethylamino]-6-Methyl-1-[cyclopropyl-(2-
Methylcarboxamidomethyl-4-Chlorophenoxy)-Acetamido]-2-Pyrazinone



- 101 -

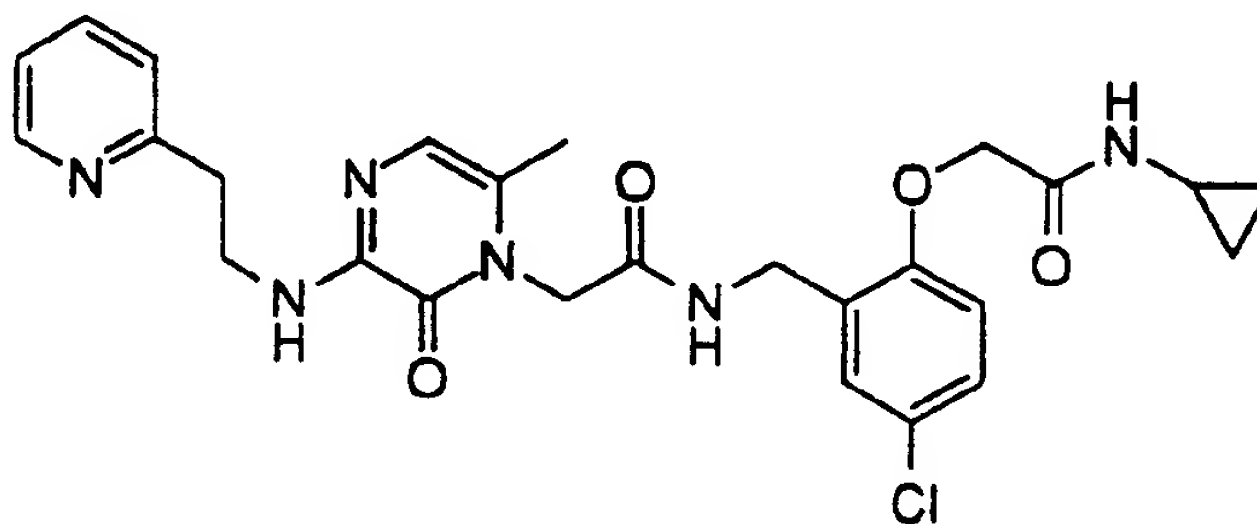
The title compound was prepared from 3-[2-(4-morpholino)ethylamino]-6-methyl-1-carboxymethylpyrazinone and cyclopropyl-2-aminomethyl-4-chlorophenoxy)-acetamide using the procedure of EXAMPLE V, Step F:

5 Analysis for $C_{25}H_{33}N_6O_5Cl \cdot 0.45 H_2O$
calc. C 55.49 H 6.31 N 15.53
found C 55.14 H 6.16 N 16.13

EXAMPLE LXX

10

3-[2-(2-Pyridyl)ethylamino]-6-Methyl-1-[cyclopropyl-(2-Methylcarboxamidomethyl-4-Chlorophenoxy)-Acetamido]-2-Pyrazinone

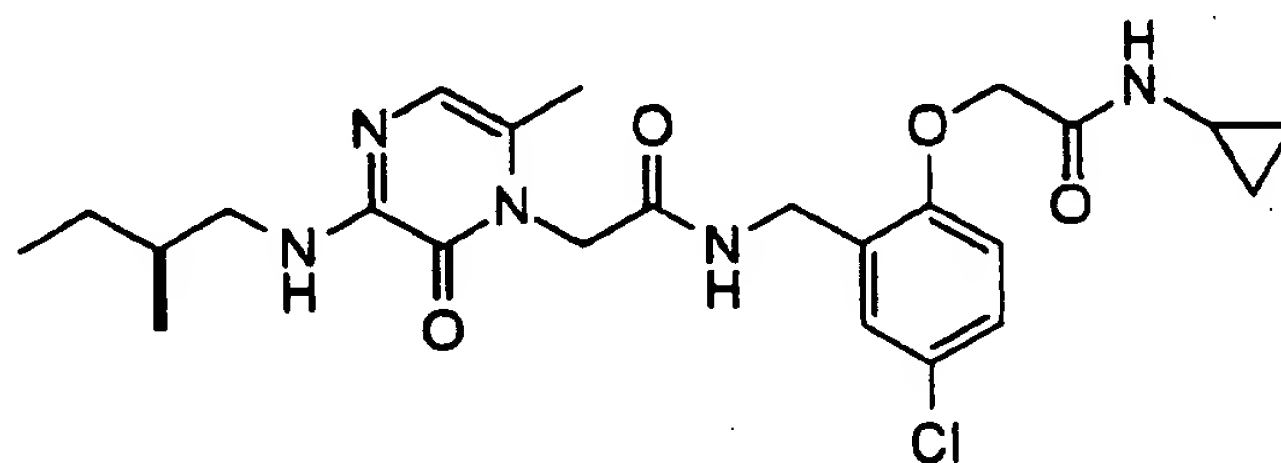


15 The title compound was prepared from 3-[2-(2-pyridyl)ethylamino]-6-methyl-1-carboxymethylpyrazinone and cyclopropyl-2-aminomethyl-4-chlorophenoxy)-acetamide using the procedure of EXAMPLE V, Step F, mp 196-199°C: MS (FAB) 525 (M+1)⁺.

- 102 -

EXAMPLE LXXI

3-[2(S)-Methyl-1-butylamino]-6-Methyl-1-[cyclopropyl-(2-Methylcarboxamidomethyl-4-Chlorophenoxy)-Acetamido]-2-Pyrazinone



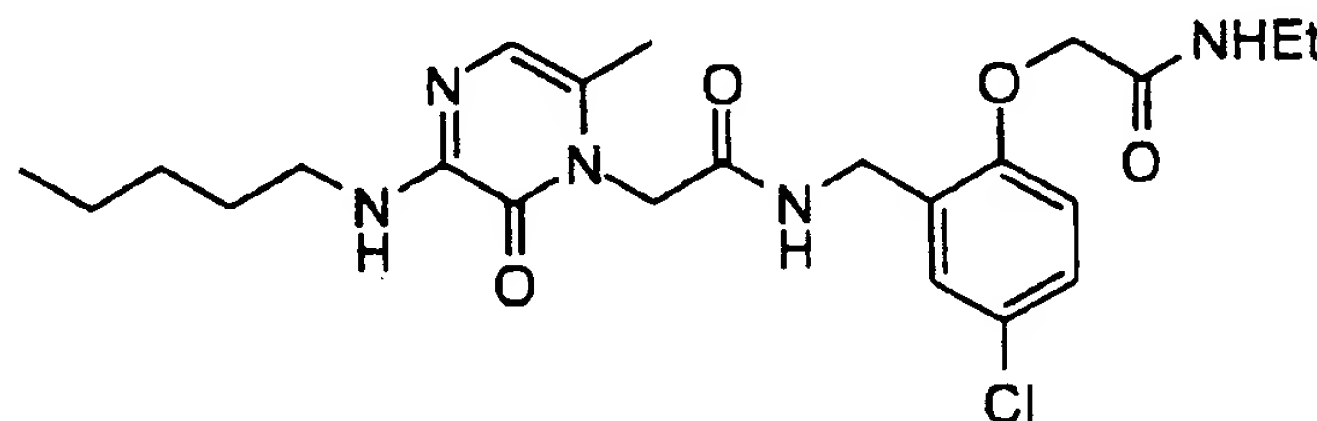
5

The title compound was prepared from 3-[2(S)-methyl-1-butylamino]-6-methyl-1-carboxymethylpyrazinone and cyclopropyl-2-aminomethyl-4-chlorophenoxy)-acetamide using the procedure of EXAMPLE V, Step F, mp 195-198°C: MS (FAB) 490 (M+1)⁺.

10

EXAMPLE LXXII

3-(1-Pentylamino)-6-Methyl-1-[ethyl-(2-Methylcarboxamidomethyl-4-Chlorophenoxy)-Acetamido]-2-Pyrazinone



15

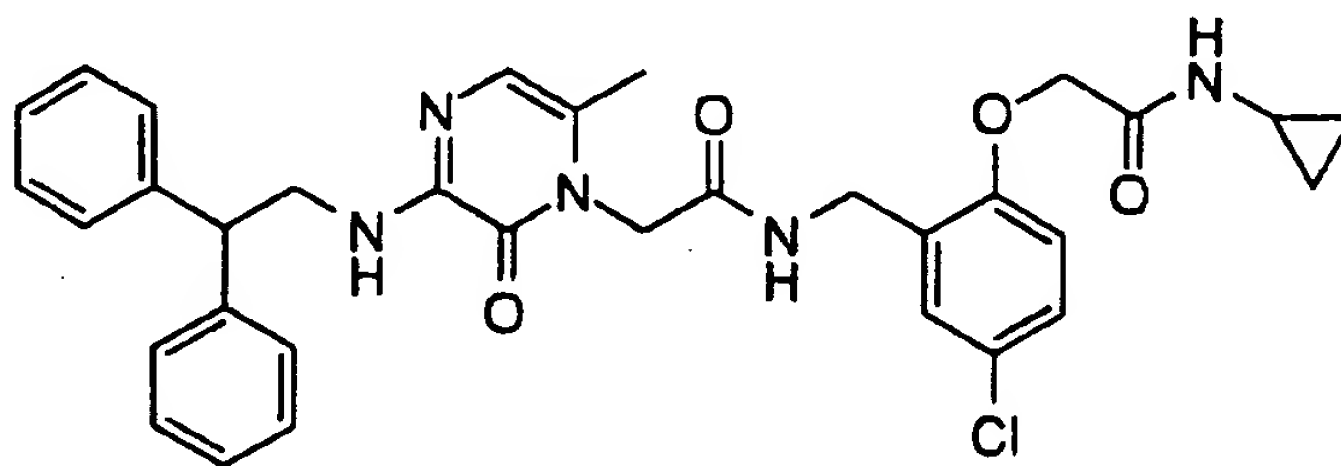
The title compound was prepared from 3-(1-pentylamino)-6-methyl-1-carboxymethylpyrazinone and ethyl-2-aminomethyl-4-chlorophenoxy)-acetamide using the procedure of EXAMPLE V, Step F, mp 125-127°C:

20

- 103 -

EXAMPLE LXXIII

3-(2,2-Diphenethylamino)-6-Methyl-1-[Cyclopropyl-(2-Methylcarboxamidomethyl-4-Chlorophenoxy)-Acetamido]-2-Pyrazinone



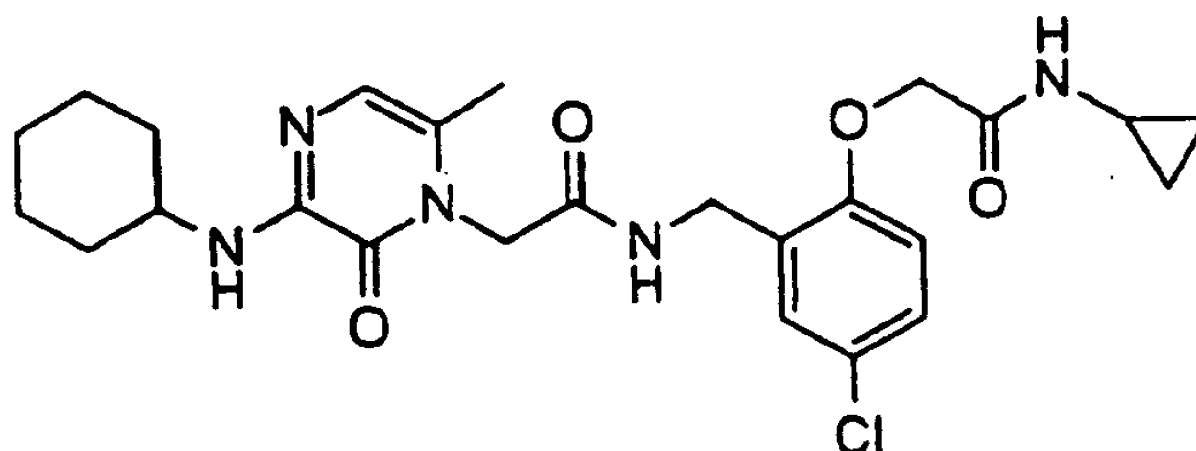
5

The title compound was prepared from 3-(1-pentylamino)-6-methyl-1-carboxymethylpyrazinone and cyclopropyl-2-aminomethyl-4-chlorophenoxy)-acetamide using the procedure of EXAMPLE V, Step F mp 153-159°C: MS (FAB) 600 (M+1)⁺.

- 104 -

EXAMPLE LXXIV

3-(Cyclohexylamino)-6-Methyl-1-[Cyclopropyl-(2-Methylcarboxamidomethyl-4-Chlorophenoxy)-Acetamido]-2-Pyrazinone



5

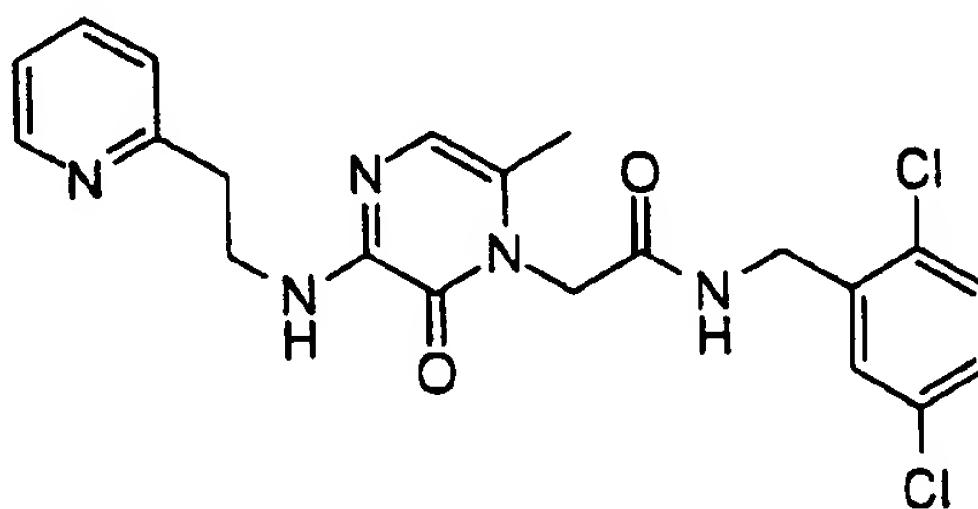
The title compound was prepared from 3-(cyclohexylamino)-6-methyl-1-carboxymethylpyrazinone and cyclopropyl-2-aminomethyl-4-chlorophenoxy)-acetamide using the procedure of EXAMPLE V, Step F, mp 114-121° C: MS (FAB) 502 (M+1)⁺.

10

EXAMPLE LXXV

3-[2-(2-Pyridyl)ethylamino]-6-Methyl-1-(2,5-Dichlorobenzyl-acetamido)-2-Pyrazinone

15



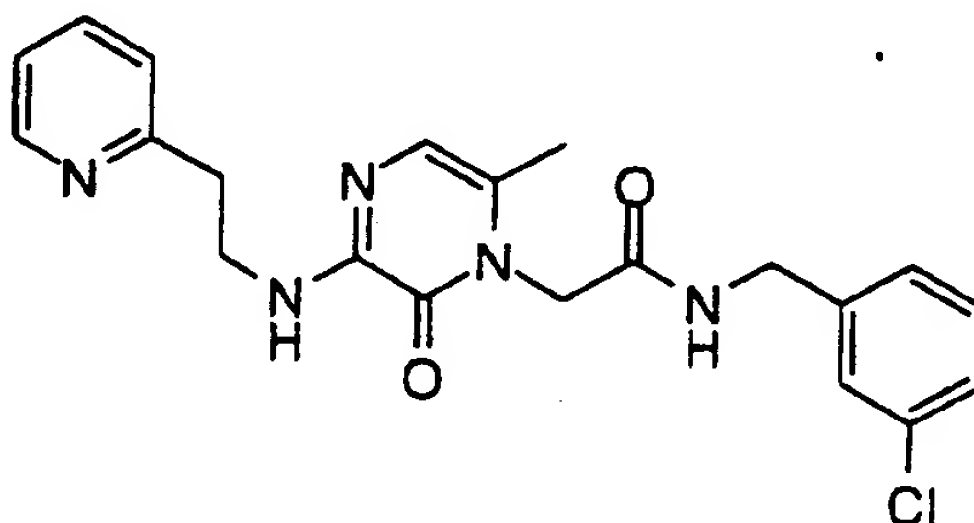
The title compound was prepared from 3-[2-(2-pyridyl)ethylamino]-6-methyl-1-carboxymethylpyrazinone and 2,5-dichlorobenzylamine using the procedure of EXAMPLE V, Step F, mp 188-191° C: MS (FAB) 446 (M+1)⁺.

20

- 105 -

EXAMPLE LXXVI

3-[2-(2-Pyridyl)ethylamino]-6-Methyl-1-(3-chlorobenzylacetamido)-2-Pyrazinone



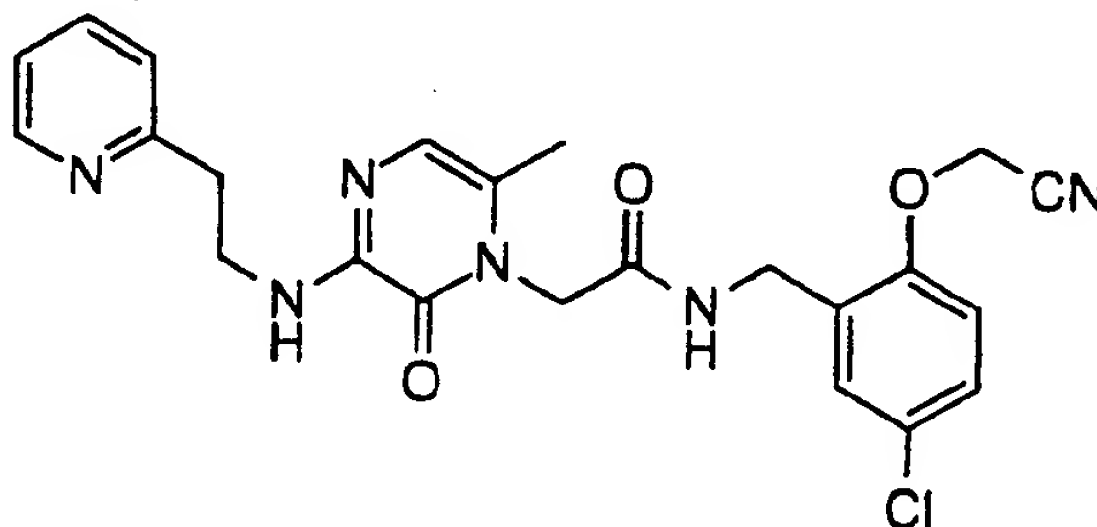
5

The title compound was prepared from 3-[2-(2-pyridyl)ethylamino]-6-methyl-1-carboxymethylpyrazinone and 3-chlorobenzylamine using the procedure of EXAMPLE V, Step F, mp 201-207°C: MS (FAB) 412 (M+1)⁺.

10

EXAMPLE LXXVII

3-[2-(2-Pyridyl)ethylamino]-6-Methyl-1-(3-chloro-6-(cyanomethoxy)benzylacetamido)-2-Pyrazinone



15

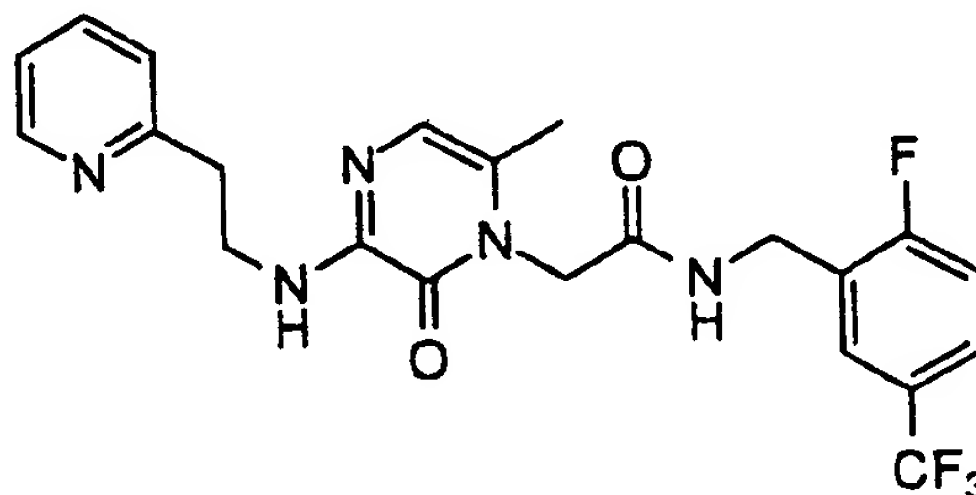
The title compound was prepared from 3-[2-(2-pyridyl)ethylamino]-6-methyl-1-carboxymethylpyrazinone and 3-chloro-6-(cyanomethoxy)benzylamine using the procedure of EXAMPLE V, Step F, mp 207-211°C.

20

- 106 -

EXAMPLE LXXVIII

3-[2-(2-Pyridyl)ethylamino]-6-Methyl-1-(2-fluoro-5-(trifluoromethyl)benzylacetamido)-2-Pyrazinone



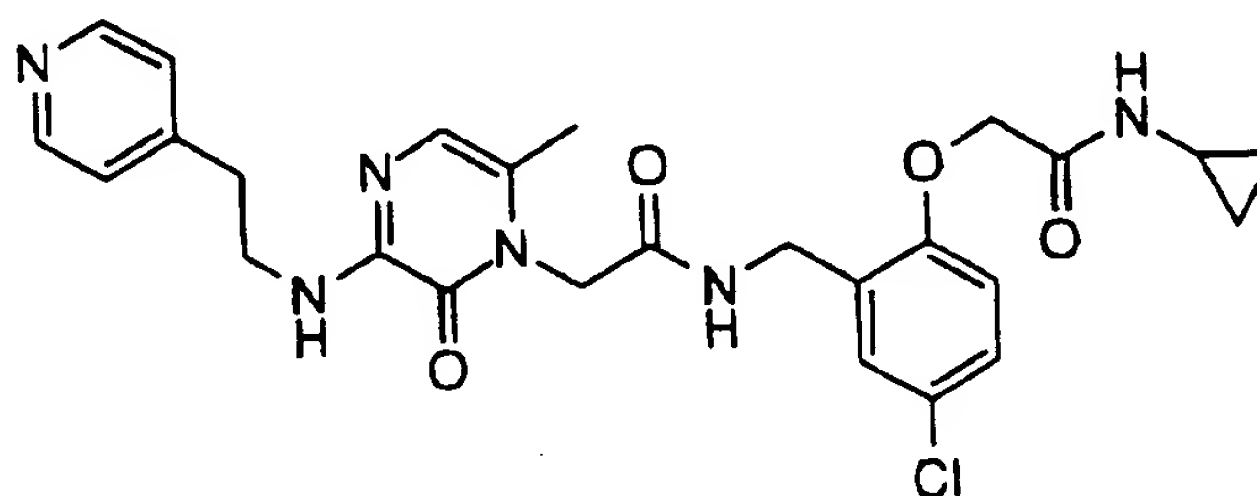
5

The title compound was prepared from 3-[2-(2-pyridyl)ethylamino]-6-methyl-1-carboxymethylpyrazinone and 2-fluoro-5-trifluoromethyl)benzylamine using the procedure of EXAMPLE V, Step F, mp 181-184°C.

10

EXAMPLE LXXIX

3-[2-(4-Pyridyl)ethylamino]-6-Methyl-1-[Cyclopropyl-(2-Methylcarboxamidomethyl-4-Chlorophenoxy)-Acetamido]-2-Pyrazinone



15

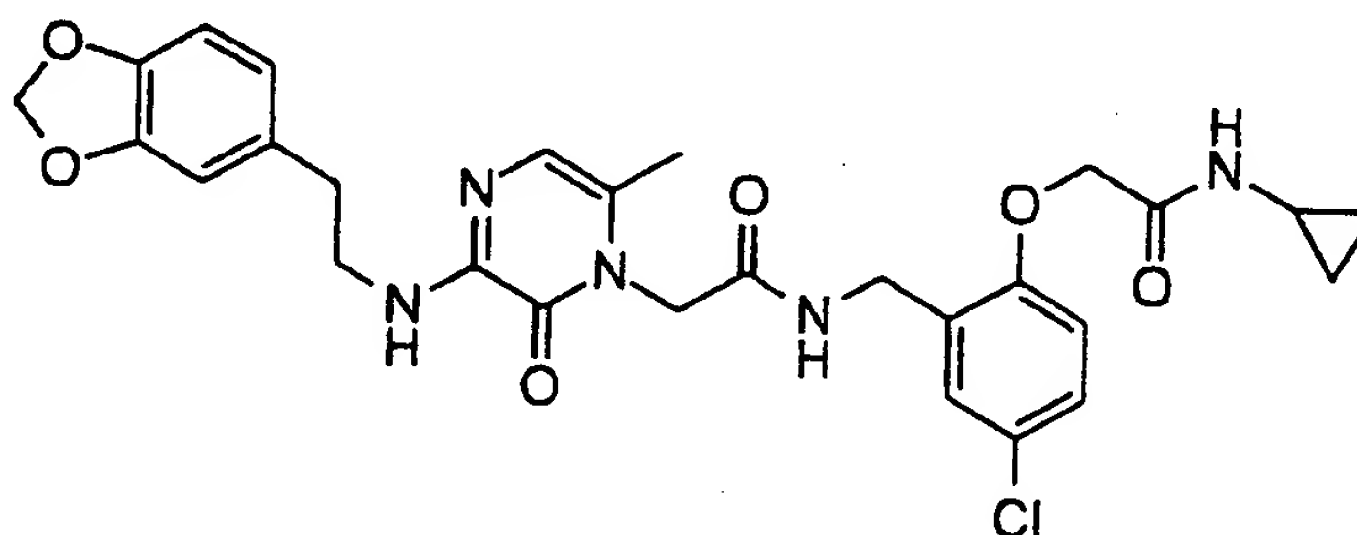
The title compound was prepared from 3-[2-(4-pyridyl)ethylamino]-6-methyl-1-carboxymethylpyrazinone and cyclopropyl-2-aminomethyl-4-chlorophenoxy)-acetamide using the procedure of EXAMPLE V, Step F, mp 190-192.5°C: MS (FAB) 525

20 (M+1)⁺.

- 107 -

EXAMPLE LXXX

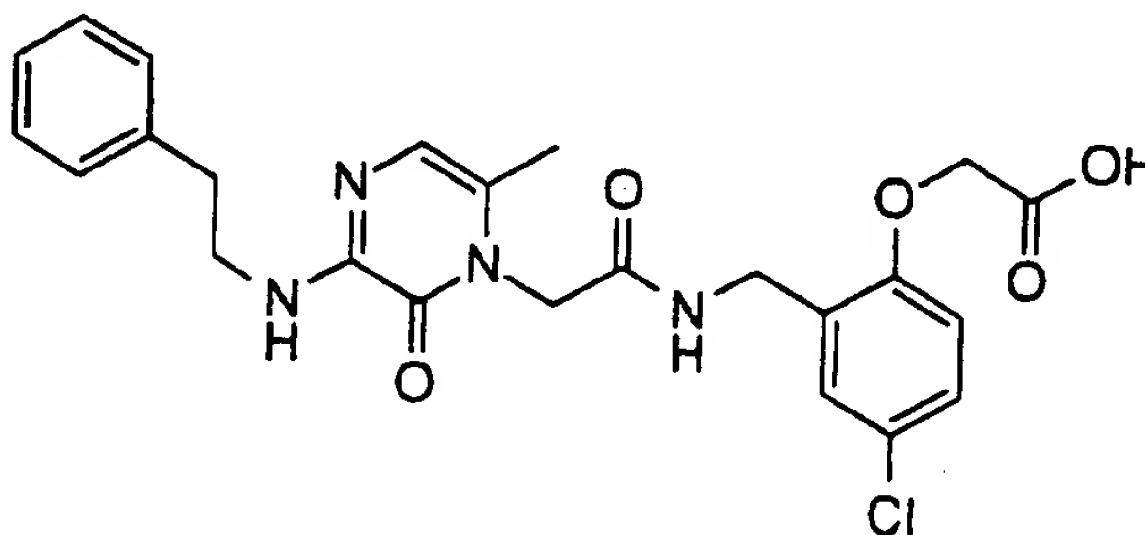
3-[2-(3,4-Methylenedioxyphenyl)ethylamino]-6-Methyl-1-[Cyclo-
propyl-(2-Methylcarboxamidomethyl-4-Chlorophenoxy)-Acetamido]-
2-Pyrazinone



The title compound was prepared from 3-[2-(3,4-methylenedioxyphenyl)ethylamino]-6-methyl-1-carboxymethylpyrazinone and cyclopropyl-2-aminomethyl-4-chlorophenoxy)-acetamide using the procedure of EXAMPLE V, Step F,
mp 202-204°C: MS (FAB) 568 (M+1)⁺.

EXAMPLE LXXXI

3-(2-Phenethylamino)-6-Methyl-1-[3-Chloro-6-(Carboxymethoxy)benzylacetamido]-2-Pyrazinone



The title compound was prepared from 3-(2-phenethylamino)-6-methyl-1-carboxymethylpyrazinone and ethyl-2-aminomethyl-4-chlorophenoxyacetate using the procedure of EXAMPLE

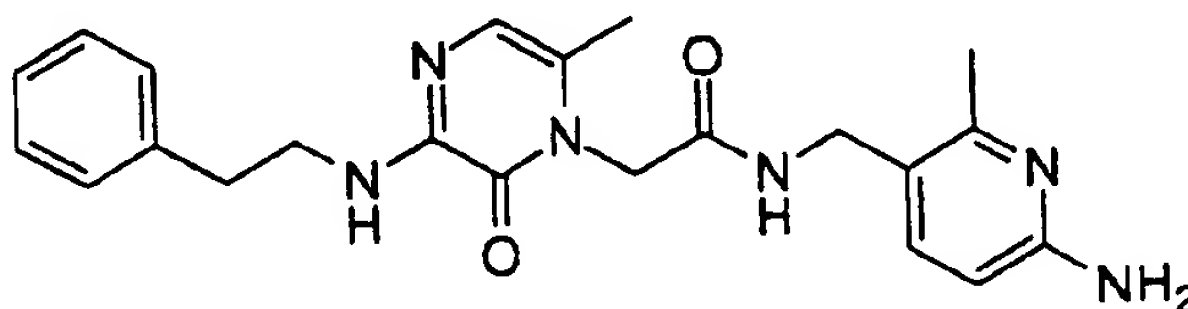
- 108 -

V, Step F, followed by a hydrolysis using the procedure of EXAMPLE V,
Step D: MS (FAB) 485 (M+1)⁺.

EXAMPLE LXXXII

5

Preparation of 3-(2-Phenylethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone



- 10 Step A: α -(Allylamino)-propionitrile hydrochloride
Concentrated HCl (20 ml, 0.24 mol) was added to a stirred solution of allylamine (36 ml, 0.48 mol) in water (100 ml) and ethanol (60 ml) at 0°C. Potassium cyanide (15 g, 0.23 mol) and acetaldehyde (11.2 ml, 0.20 mol) were then added and the mixture was heated to reflux. After 15 h the volatiles were removed *in vacuo* and the residual solution was saturated with NaCl and was extracted with methylene chloride (3 times). The combined extracts were dried (Na₂SO₄) and evaporated *in vacuo* to an oil which was dissolved in 1 M HCl (200 ml). The solution was evaporated *in vacuo*, azeotroping with 1:1 toluene/methanol to give a solid which was heated to reflux in ethyl acetate (200 ml), cooled, filtered and dried to give the title compound as the HCl salt: ¹H NMR (400 MHz, CD₃OD) δ 1.72 (d, J = 7.0 Hz, 3H, CH₃), 3.78-3.90 (m, 2H, CH₂), 4.63 (q, J=7.0 Hz, a-CH), 5.56-5.66 (m, 2H, CHCH₂), 5.91-6.02 (m, 1H, CHCH₂).
- 25 Step B: 1-Allyl-3,5-dichloro-6-methylpyrazinone
A stirred mixture of oxalyl chloride (30.5 ml, 0.35 mol) and α -(allylamino)-propionitrile hydrochloride (10.26 g, 70 mmol) in *o*-dichlorobenzene (100 ml) was heated to 100°C for 15 h. The solvent was evaporated *in vacuo* and the residual black oil was purified by flash

- 109 -

column chromatography on silica (eluting with 30% ethyl acetate hexanes) to give the title compound as a tan crystalline solid:

¹H NMR (400 Mz, CDCl₃) δ 2.48 (s, 3H, CH₃), 4.75 (m, 2H, NCH₂), 5.18 (m, 1H, CHCH_AH_B), 5.33 (m, 1H, CHCH_AH_B), 5.85-5.92 (m, 1H, CHCH_AH_B).

Step C: 3,5-Dichloro-6-methyl-1-methylenecarboxypyrazinone

Ruthenium trichloride hydrate (114 mg, 0.547 mmol) was added to a stirred mixture of 1-allyl-3,5-dichloro-6-methylpyrazinone (5.45 g, 24.88 mmol) and sodium periodate (21.82 g, 0.102 mol) in water (75 ml), acetonitrile (50 ml) and carbon tetrachloride (50 ml). After 3 h the reaction mixture was extracted with methylene chloride (4 times) and the combined extracts were dried (Na₂SO₄) and evaporated *in vacuo* to a syrup. The ¹H NMR (CDCl₃) of this material showed it to be a 1:1 mixture of the acid and the aldehyde. The crude mixture was dissolved in acetone (50 ml) and Jones Reagent (2.7 M) was added until the reaction remained orange. The reaction was then extracted into ethyl acetate which was then washed with brine, dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound as a tan solid:

¹H NMR (400 Mz, DMSO) δ 2.41 (s, 3H, Me), 4.86 (s, 2H, CH₂).

Step D: 3-(2-Phenethylamino)-5-chloro-6-methyl-1-methylene-carboxypyrazinone

Phenethylamine (0.80 ml, 6.33 mmol) was added to a stirred solution of 3,5-dichloro-6-methyl-1-methylenecarboxypyrazinone (0.50-g, 2.11 mmol) in dioxane (6 ml) and the resulting solution was warmed to 60°C. After 16 h the reaction mixture was partitioned between methylene chloride and 10% citric acid solution. The organic layer was dried (Na₂SO₄) and evaporated *in vacuo* to give a tan solid which was purified by flash column chromatography (eluting with a methanol/chloroform/2% acetic acid gradient, 2-5% methanol) to give after azeotroping dry with toluene the title compound as a white solid:

- 110 -

¹H NMR (300 Mz, DMSO) δ 2.19 (s, 3H, Me), 2.84 (t, J = 7.0 Hz, 2H, PhCH₂), 3.45 (q, J = 7.0 Hz, 2H, CH₂NH), 4.70 (s, 2H, CH₂CO₂), 7.18-7.31 (m, 5H, Ph), 7.46 (br t, 1H, NH).

5 Step E: 3-(2-Phenethylamino)-6-methyl-1-methylene-carboxypyrazinone

Raney nickel alloy (1 g) was added to a stirred solution of 3-(2-phenethylamino)-5-chloro-6-methyl-1-methylenecarboxypyrazinone (158 mg, 0.49 mmol) in 1:1 methanol/1 M NaOH (24 ml). After 2 h the reaction mixture was filtered through celite, washing with 1:1 methanol/water and the filtrate was evaporated *in vacuo* to a white solid. This crude product, which was contaminated by inorganic salts, was purified by preparative HPLC (C18, water/acetonitrile/ 0.1% TFA gradient) to give the title compound as a foam:

15 ¹H NMR (400 Mz, DMSO) δ 2.11 (s, 3H, Me), 2.87 (t, J = 7.6 Hz, 2H, PhCH₂), 3.53 (br s, 2H, CH₂NH), 4.68 (s, 2H, CH₂CO₂), 6.68 (s, 1H, pyrazinone H-5), 7.20-7.31 (m, 5H, Ph), 8.16 (br s, 1H, NH).

20 Step F: 3-(2-Phenethylamino)-6-methyl-1-(2-t-butoxycarbonylamino-6-methyl-5-methylenecarboxamidomethyl-pyridinyl)-pyrazinone

EDC Hydrochloride (56 mg, 0.29 mmol) was added to a stirred mixture of 3-(2-phenethylamino)-6-methyl-1-methylene-carboxypyrazinone (91 mg, 0.23 mmol), HOBT (40 mg, 0.29 mmol), 5-aminomethyl-2-t-butoxycarbonylamino-6-methylpyridine (70 mg, 0.29 mmol) and N-methylmorpholine (0.13 ml, 1.17 mmol) in DMF (1 ml) and the mixture was stirred for 16 h. The reaction was diluted with ethyl acetate and was washed with water, dried (Na₂SO₄) and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (ethylacetate/hexanes gradient, 80-100% ethyl acetate), to give the title compound:

30 ¹H NMR (300 Mz, CDCl₃) δ 1.51 (s, 9H, t-Bu), 2.26 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 2.93 (t, J = 7.0 Hz, PhCH₂), 3.65 (q, J = 7.0 Hz, PhCH₂CH₂), 4.36 (d, J = 5.6 Hz, 2H, CONHCH₂), 4.61 (s, 2H,

- 111 -

CH₂CO), 5.91 (br t, 1H, NH), 6.65 (br t, 1H, NH), 6.77 (s, 1H, pyrazinone H-5), 7.12 (s, 1H, NHBOC), 7.21-7.32 (m, 5H, Ph), 7.42 (d, J = 8.5 Hz, 1H, pyridine H-3), 7.68 (d, J = 8.5 Hz, 1H, pyridine H-4).

5 Step G: 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-pyrazinone

HCl gas was bubbled through a stirred suspension of 3-(2-phenethyl-amino)-6-methyl-1-(2-t-butoxycarbonylamino-6-methyl-5-methylene-carboxamidomethylpyridinyl)-pyrazinone (85 mg, 0.17 mmol) in ethyl acetate (10 ml) at 0°C until a solution had formed which was saturated with HCl. After 2 h at RT the mixture was degassed with nitrogen and filtered to give the title compound as a bis HCl salt white crystalline solid, m.p. >200°C:

¹H NMR (300 Mz, CD₃OD) δ 2.18 (s, 3H, CH₃), 2.52 (s, 3H, CH₃), 3.00 (t, J = 7.4 Hz, PhCH₂), 3.68 (t, J = 7.4 Hz, PhCH₂CH₂), 4.33 (d, J = 5.4 Hz, 2H, CONHCH₂), 4.76 (s, 2H, CH₂CO), 6.55 (s, 1H, pyrazinone H-5), 6.84 (d, J = 9.3 Hz, 1H, pyridine H-3), 7.23-7.31 (m, 5H, Ph), 7.86 (d, J = 9.3 Hz, 1H, pyridine H-4); MS (FAB) 407 (M+1)⁺.

20 IN VITRO ASSAY FOR DETERMINING PROTEINASE INHIBITION

Assays of human α-thrombin and human trypsin were performed by the methods substantially as described in Thrombosis Research, Issue No. 70, page 173 (1993) by S.D. Lewis *et al.*

25 The assays were carried out at 25°C in 0.05 M TRIS buffer pH 7.4, 0.15 M NaCl, 0.1% PEG. Trypsin assays also contained 1 mM CaCl₂. In assays wherein rates of hydrolysis of a *p*-nitroanilide (pna) substrate were determined, a Thermomax 96-well plate reader was used was used to measure (at 405 nm) the time dependent appearance of *p*-nitroaniline. sar-PR-pna was used to assay human α-thrombin (K_m=125 μM) and bovine trypsin (K_m=125 μM). *p*-Nitroanilide substrate concentration was determined from measurements of absorbance at 342 nm using an extinction coefficient of 8270 cm⁻¹M⁻¹.

- 112 -

In certain studies with potent inhibitors ($K_i < 10$ nM) where the degree of inhibition of thrombin was high, a more sensitive activity assay was employed. In this assay the rate of thrombin catalyzed hydrolysis of the fluorogenic substrate Z-GPR-afc ($K_m = 27$ μ M) was
5 determined from the increase in fluorescence at 500 nm (excitation at 400 nm) associated with production of 7-amino-4-trifluoromethyl coumarin. Concentrations of stock solutions of Z-GPR-afc were determined from measurements of absorbance at 380 nm of the 7-amino-4-trifluoromethyl coumarin produced upon complete hydrolysis of an aliquot of the stock
10 solution by thrombin.

Activity assays were performed by diluting a stock solution of substrate at least tenfold to a final concentration $\leq 0.1 K_m$ into a solution containing enzyme or enzyme equilibrated with inhibitor. Times required to achieve equilibration between enzyme and inhibitor were
15 determined in control experiments. Initial velocities of product formation in the absence (V_o) or presence of inhibitor (V_i) were measured. Assuming competitive inhibition, and that unity is negligible compared $K_m/[S]$, $[I]/e$, and $[I]/e$ (where $[S]$, $[I]$, and e respectively represent the total concentrations, of substrate, inhibitor and enzyme), the equilibrium
20 constant (K_i) for dissociation of the inhibitor from the enzyme can be obtained from the dependence of V_o/V_i on $[I]$ shown in equation 1.

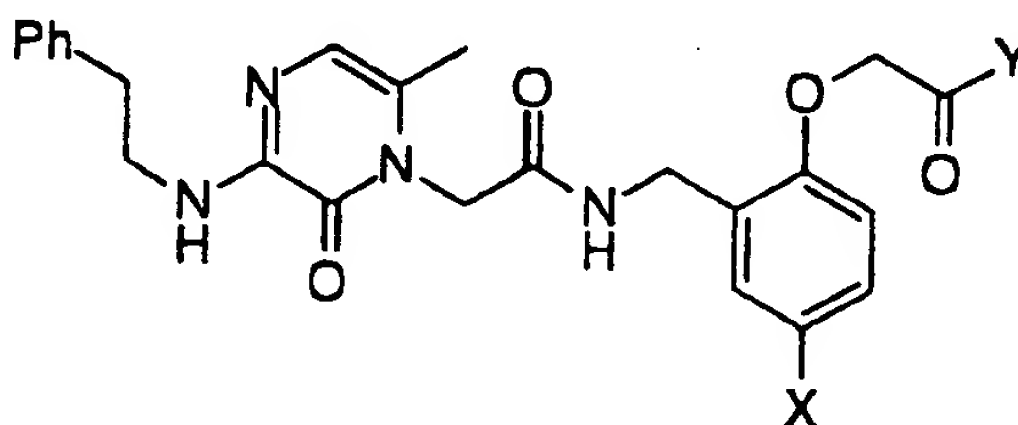
$$V_o/V_i = 1 + [I]/K_i \quad (1)$$

25 The activities shown by this assay indicate that the compounds of the invention are therapeutically useful for treating various conditions in patients suffering from unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated
30 intravascular coagulation, and reocclusion or restenosis of recanalized vessels. The inhibitory activity of compounds of the invention against human thrombin, represented by K_i , is less than 24 nM. These are selective compounds, as evidenced by their inhibitory activity against human trypsin (represented by K_i), which is at least 1000 nM.

- 113 -

The following tables illustrate additional compounds within the scope of the present invention. Inhibitory activity is represented by "*", indicating K_i greater than or equal to 1 nM, or "**", indicating K_i less than 1 nM.

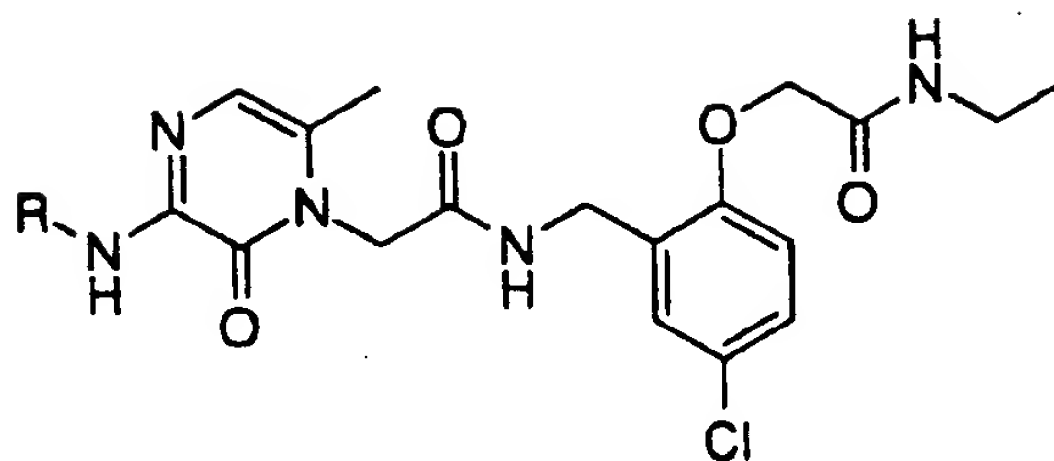
5

TABLE 1

X	Y	Ki
H	NHC ₂ H ₅	**
H	NHC ₃ H ₅	
H	NH(CH ₂) ₂ N(CH ₃) ₂	
F	NHC ₂ H ₅	
F	NHC ₃ H ₅	
F	NH(CH ₂) ₂ N(CH ₃) ₂	

10

- 114 -

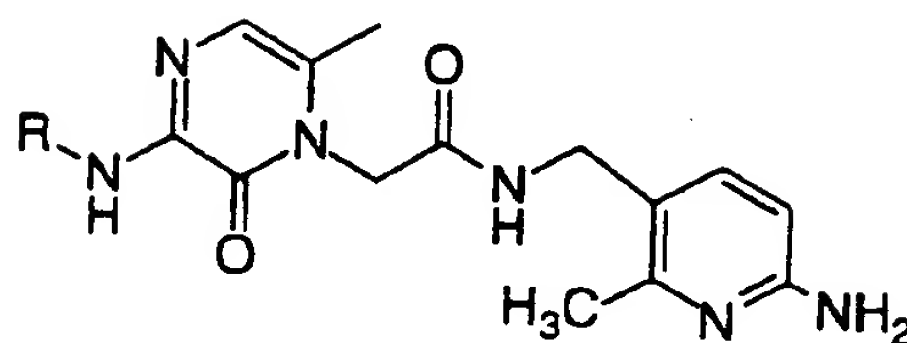
TABLE 2

R

Ki

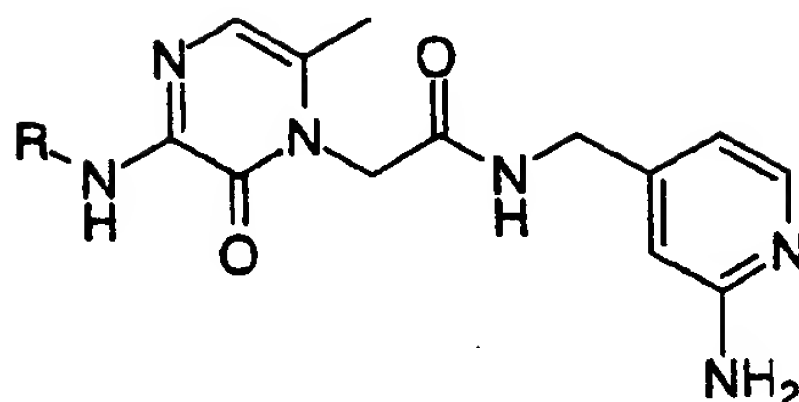
C₃H₅C₃H₅CH₂t-C₄H₉HO₂CCH₂CF₃CH₂(CH₃)₂N(CH₂)₂

- 115 -

TABLE 3

R	Ki
PhCH ₂ C(CH ₃) ₂	*
PhCHCH ₃	
PhCH ₂ CHCO ₂ H	
n-C ₆ H ₁₃	

- 116 -

TABLE 4

R

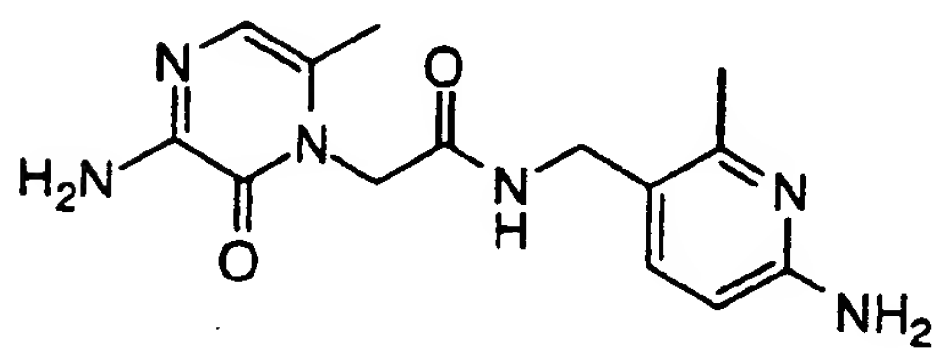
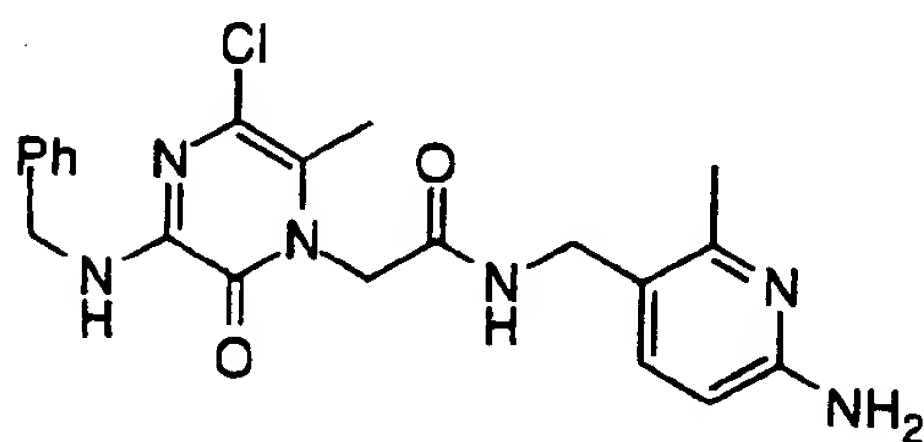
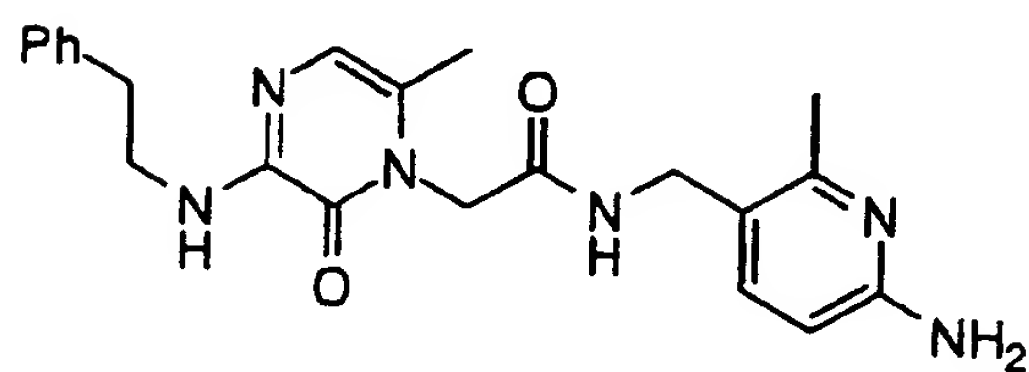
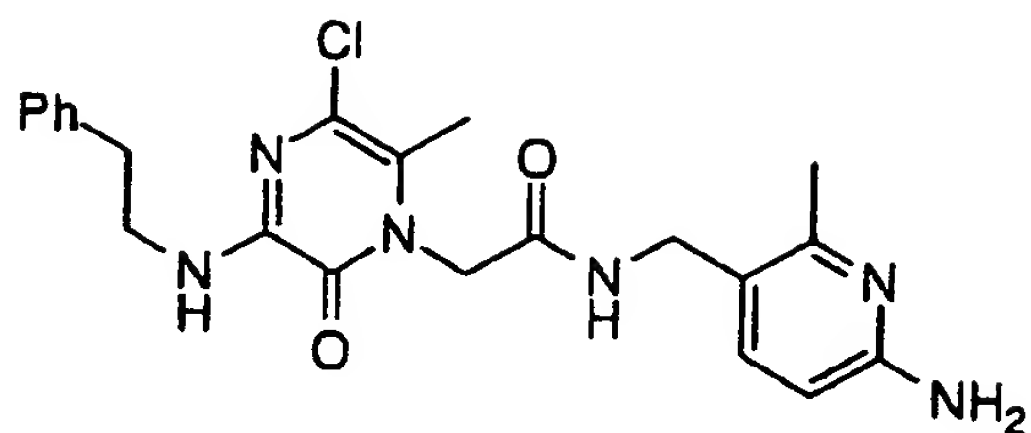
PhCH₂C(CH₃)₂PhCHCH₃PhCH₂CHCO₂Hn-C₆H₁₃

5

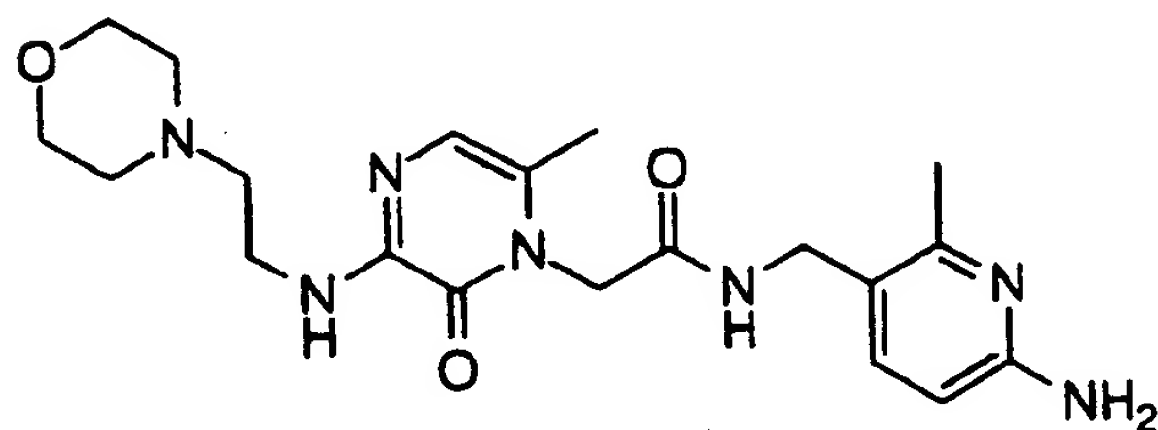
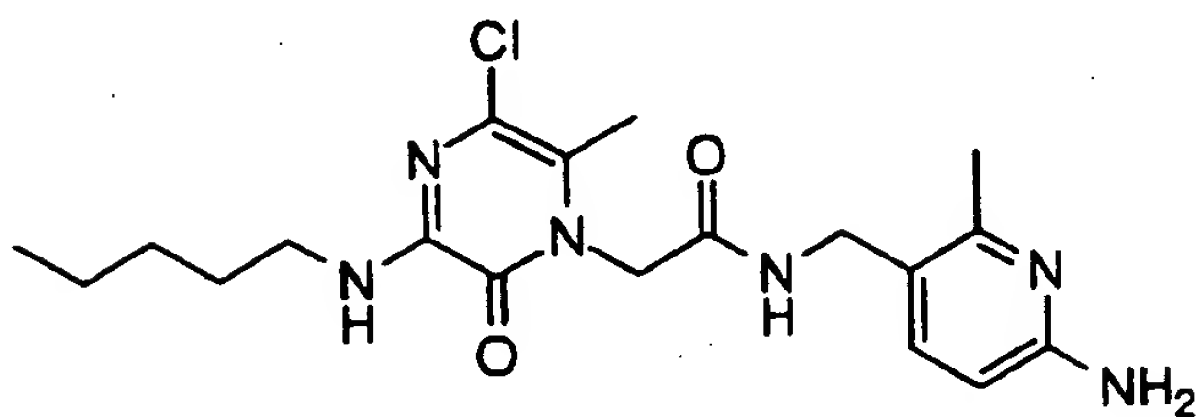
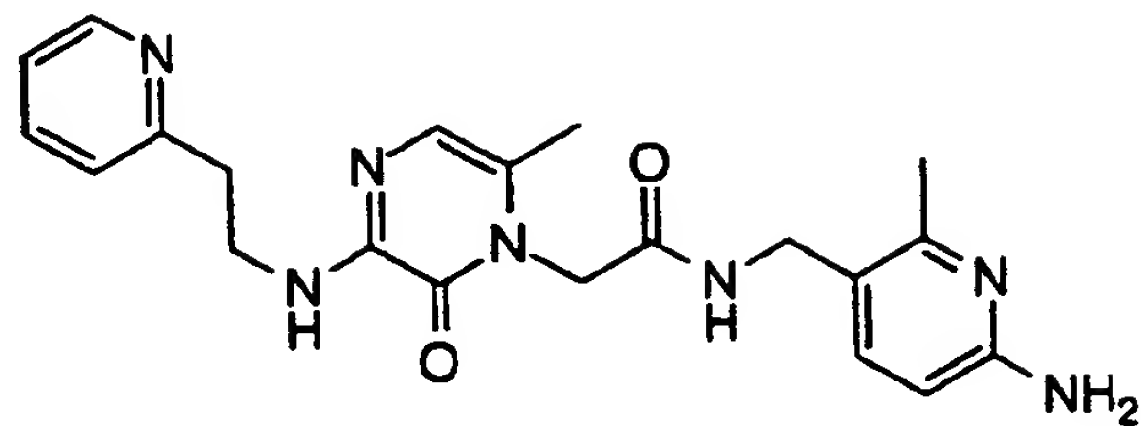
Additional exemplary compounds of the invention, with associated inhibitory activity of the compounds against human thrombin, (represented by Ki) are shown below. As in the tables above, inhibitory activity is represented by "*", indicating Ki greater than or equal to 1 nM, or "**", indicating Ki less than 1 nM.

10

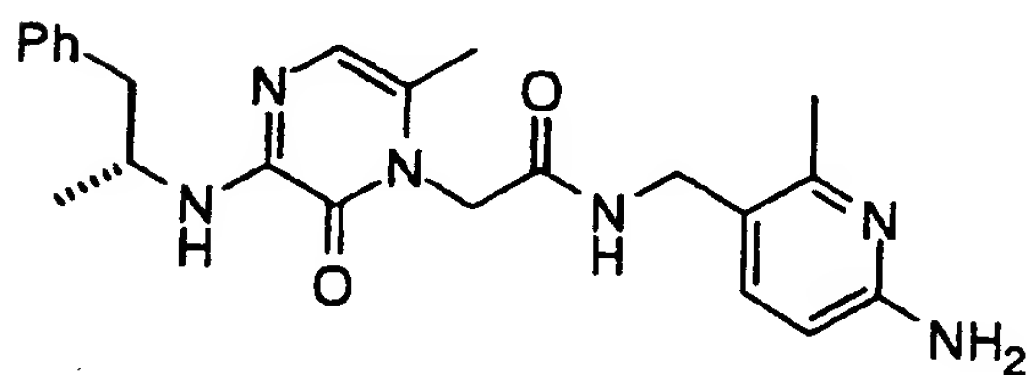
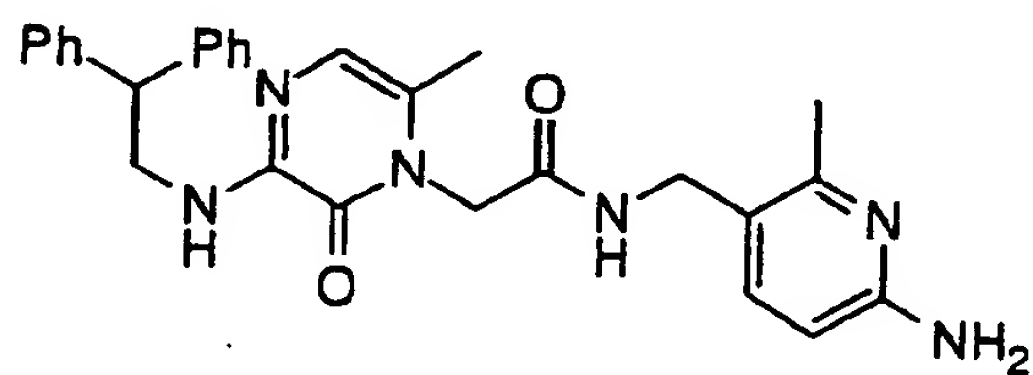
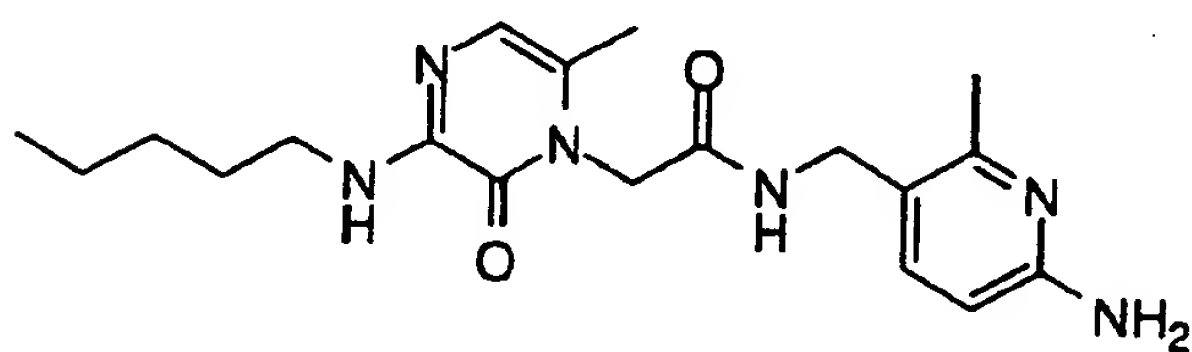
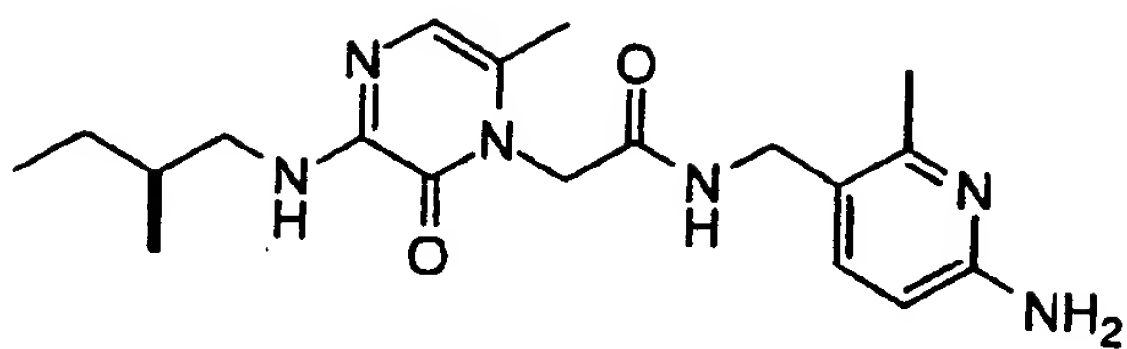
- 117 -



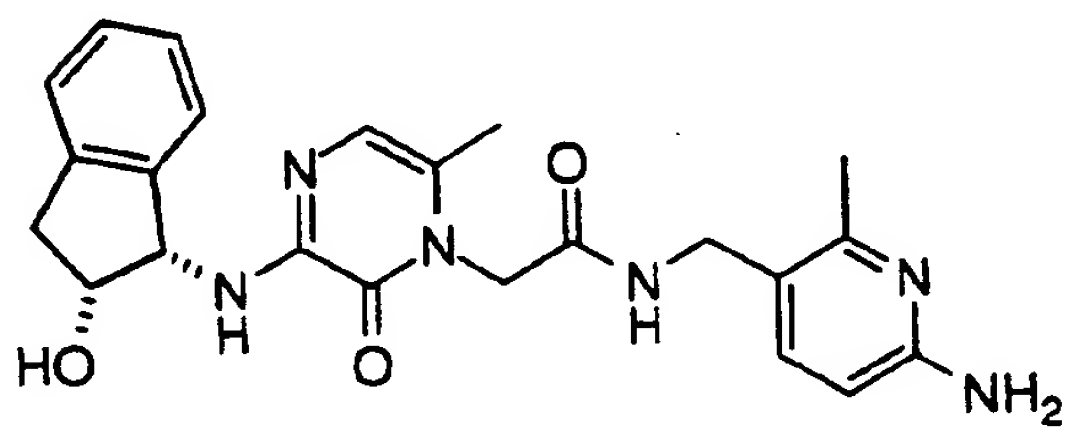
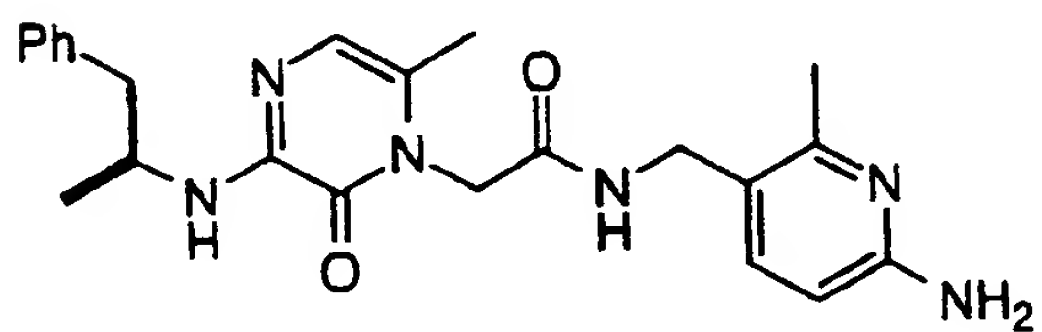
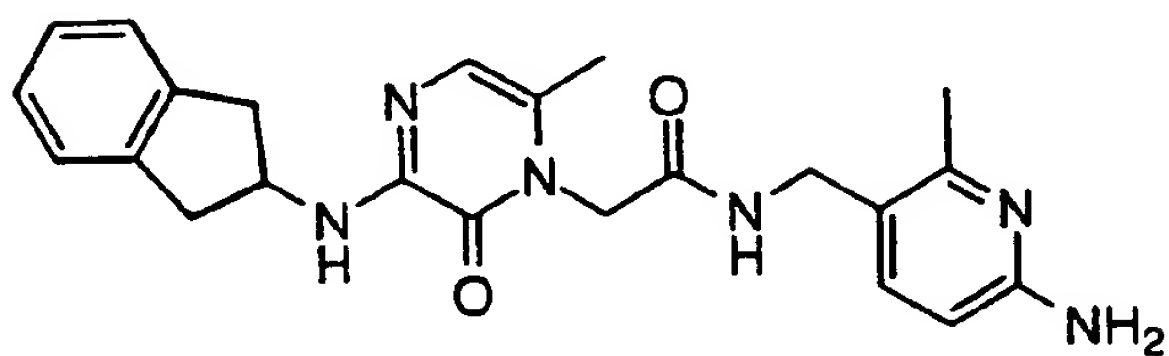
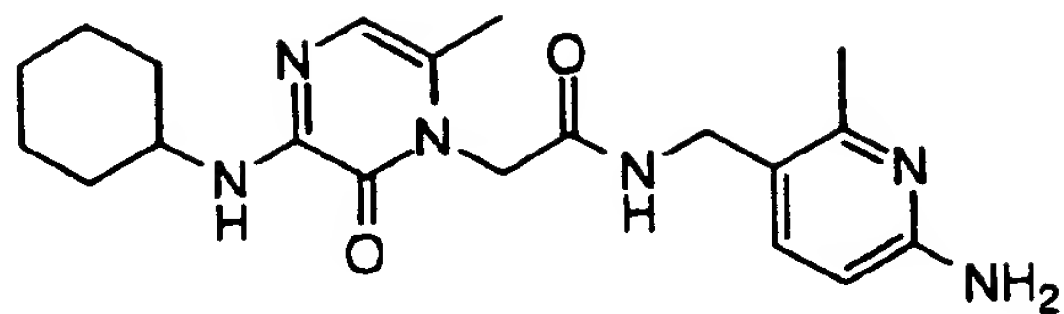
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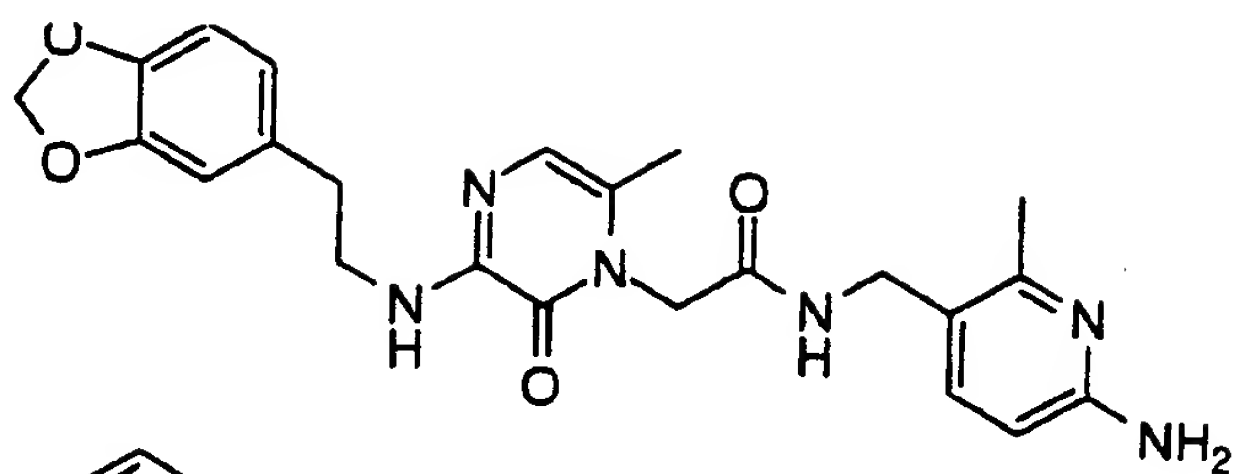
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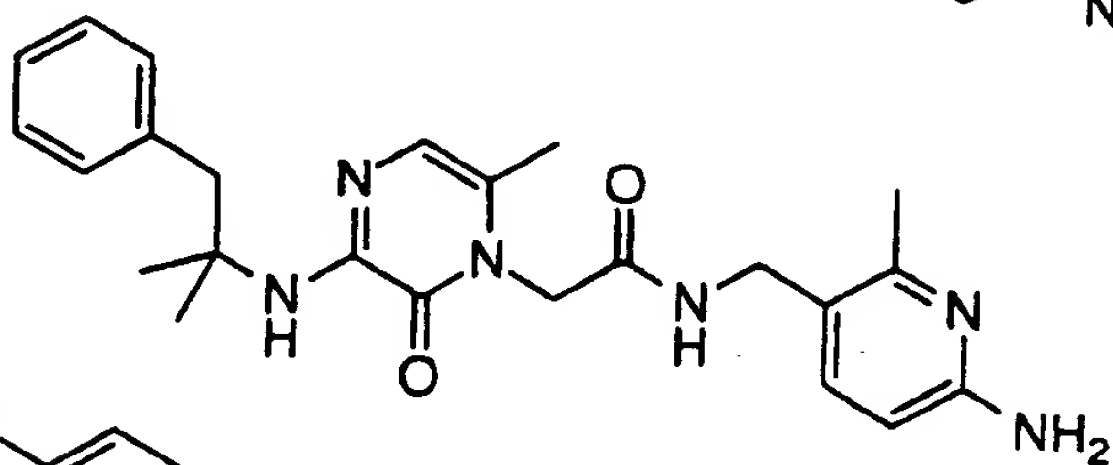
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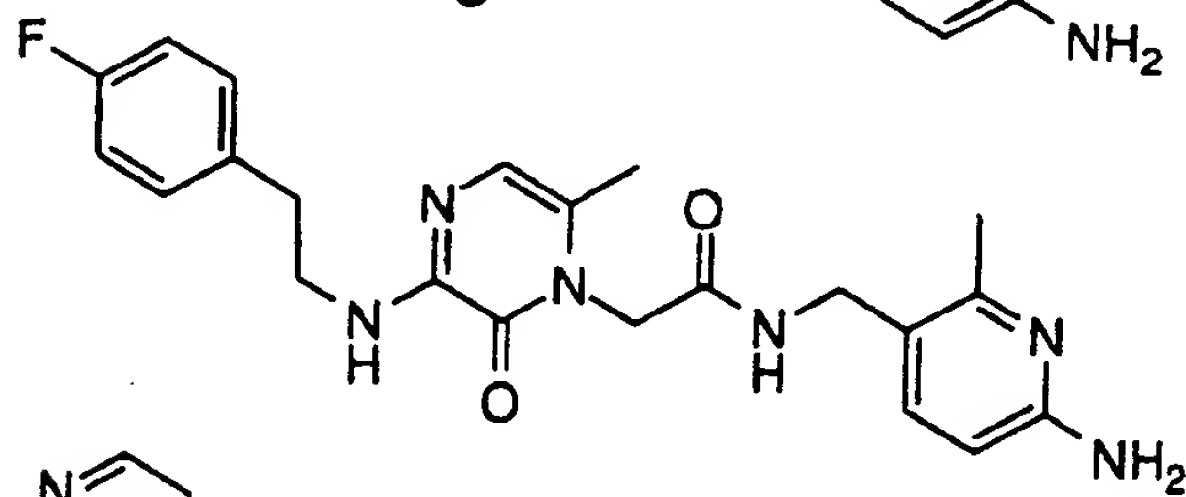
- 121 -



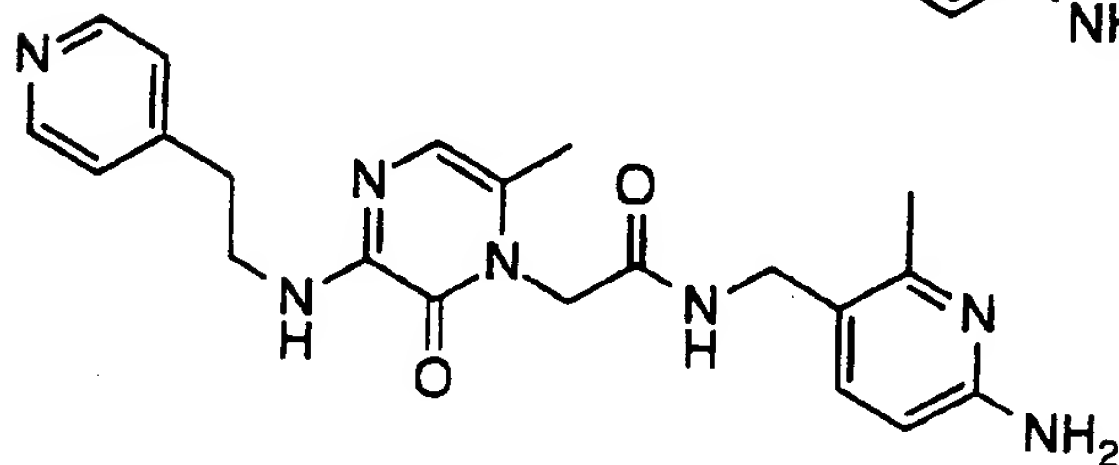
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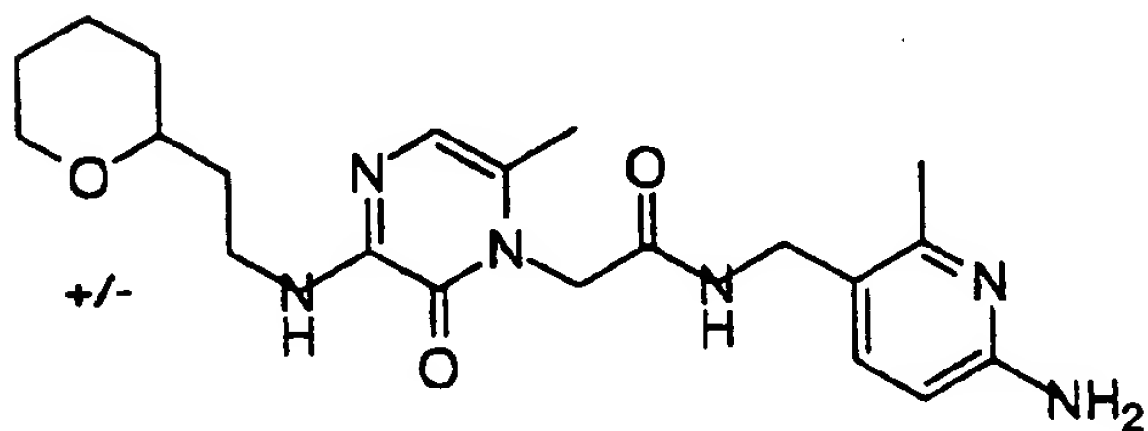
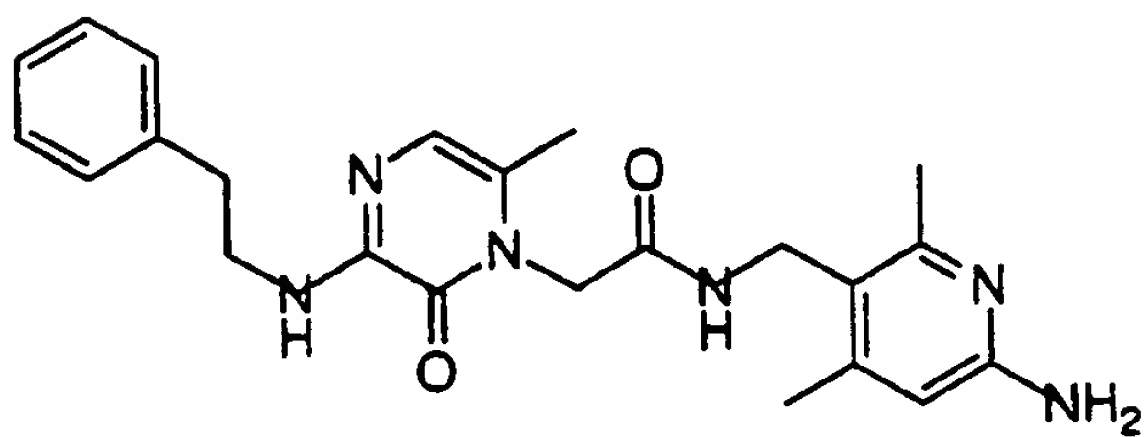
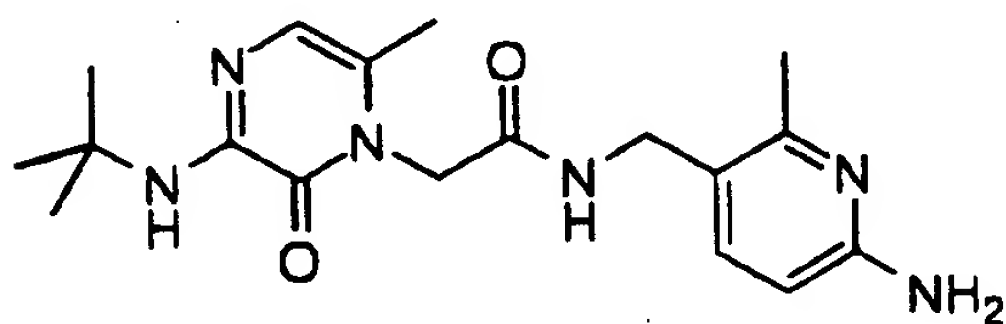
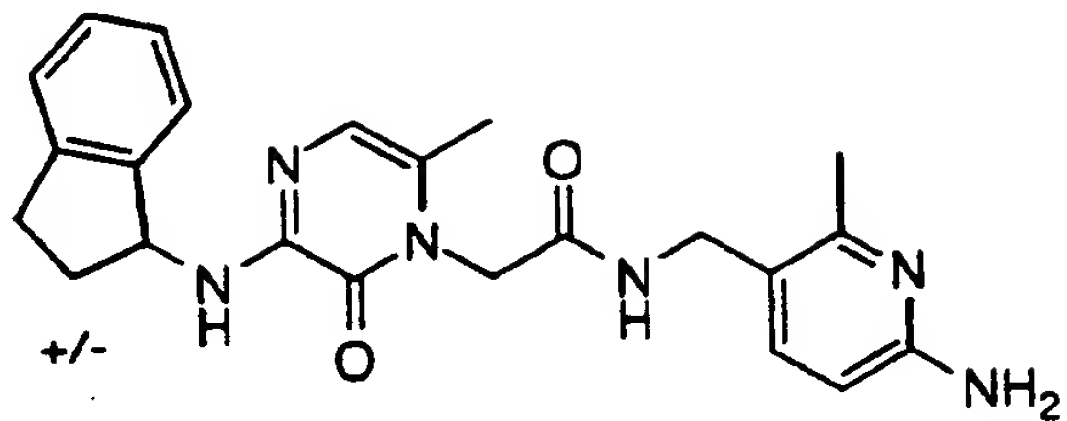


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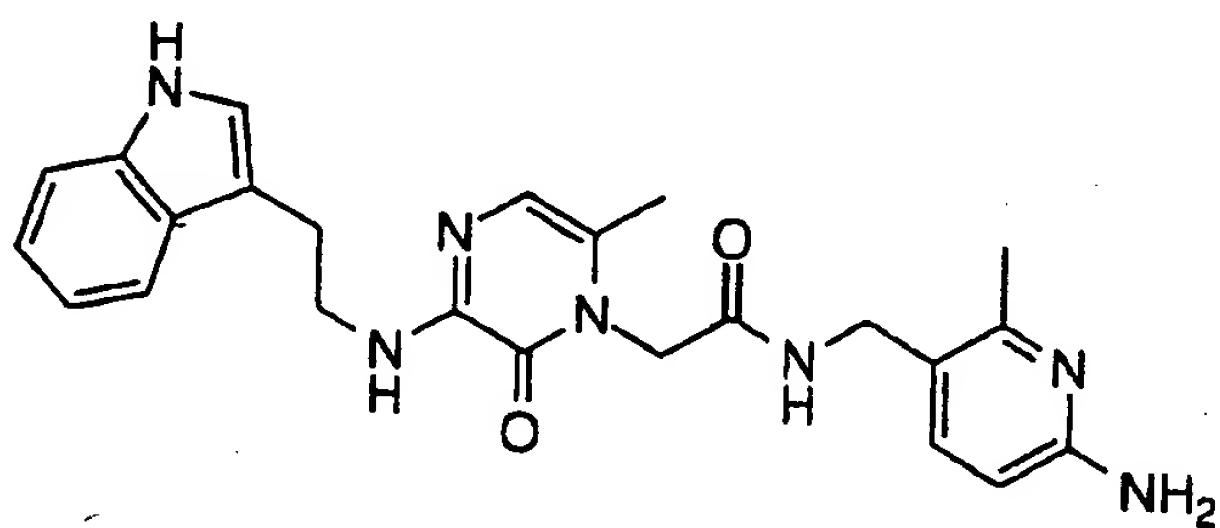
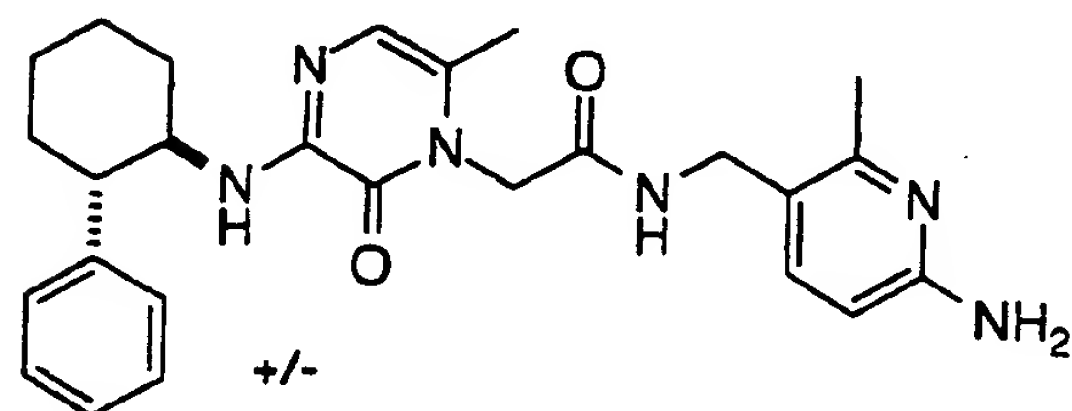
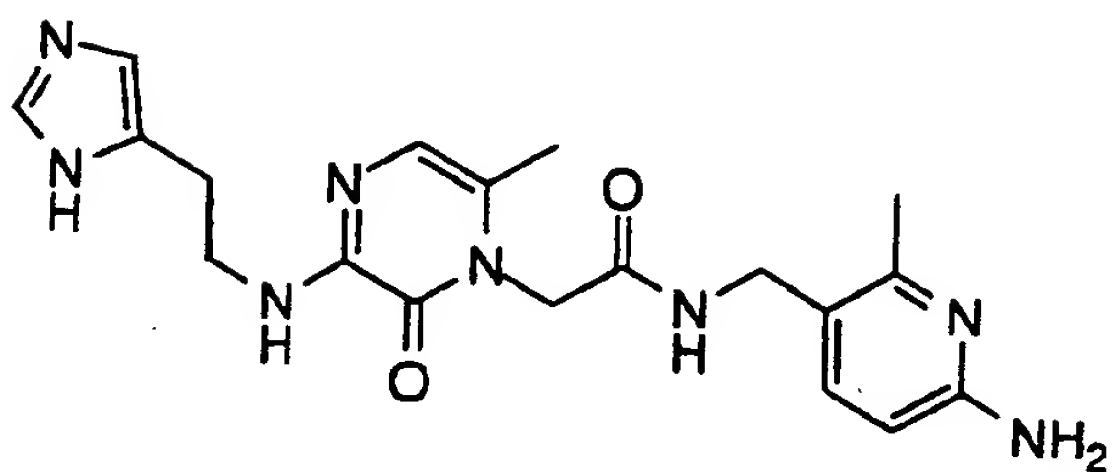
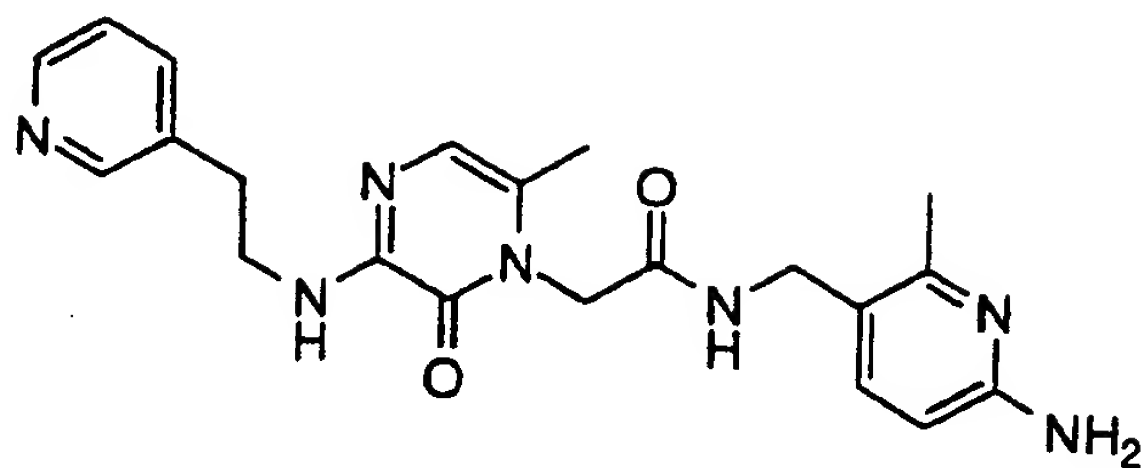


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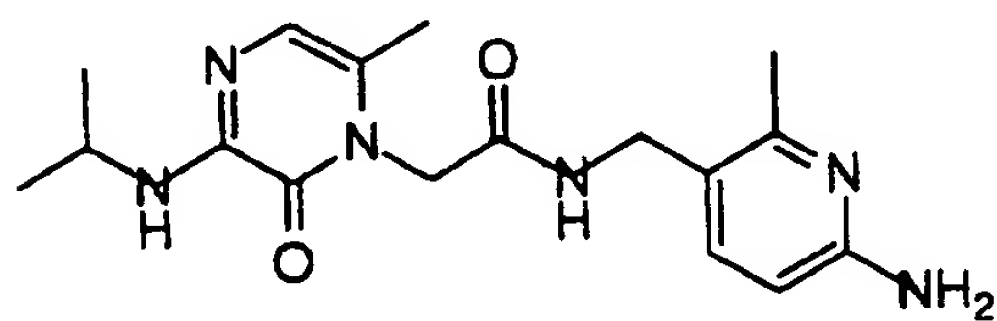
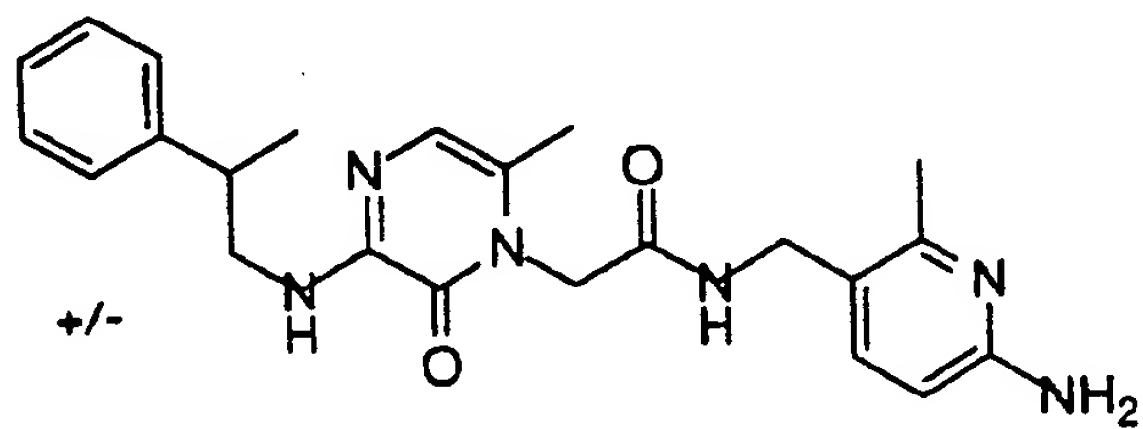
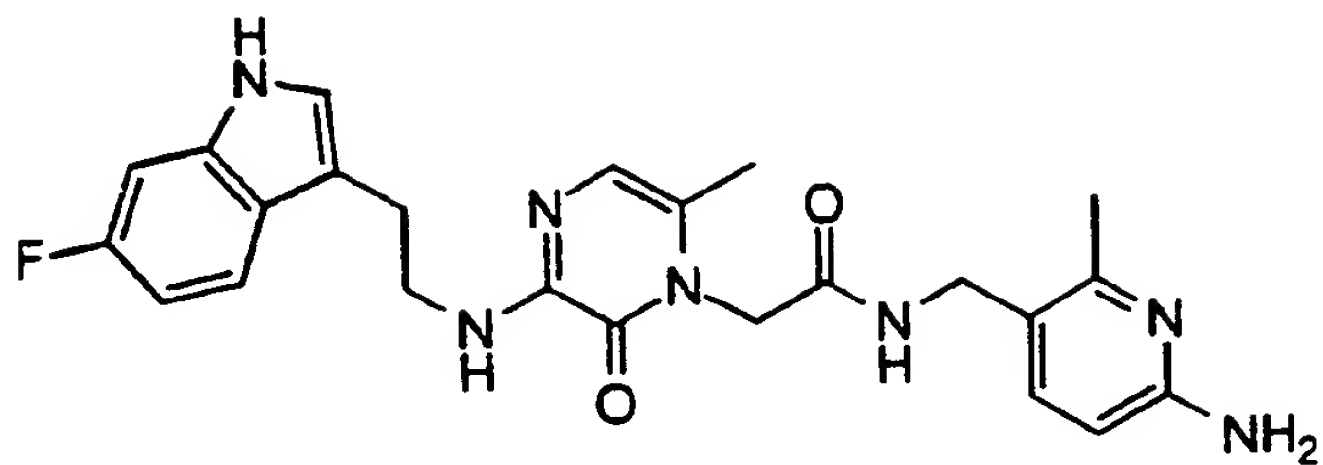
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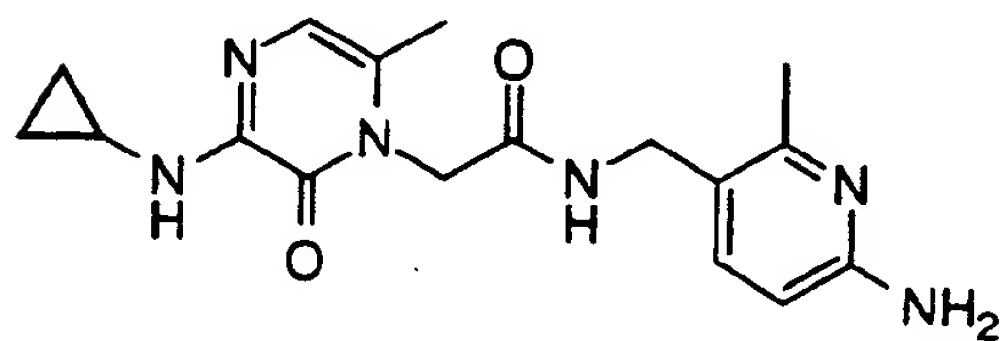
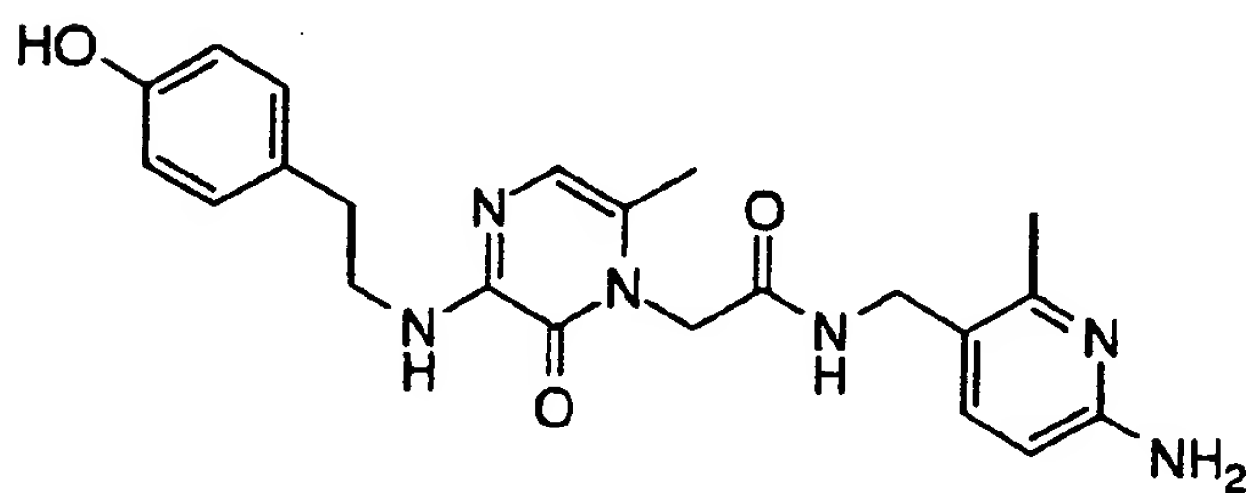
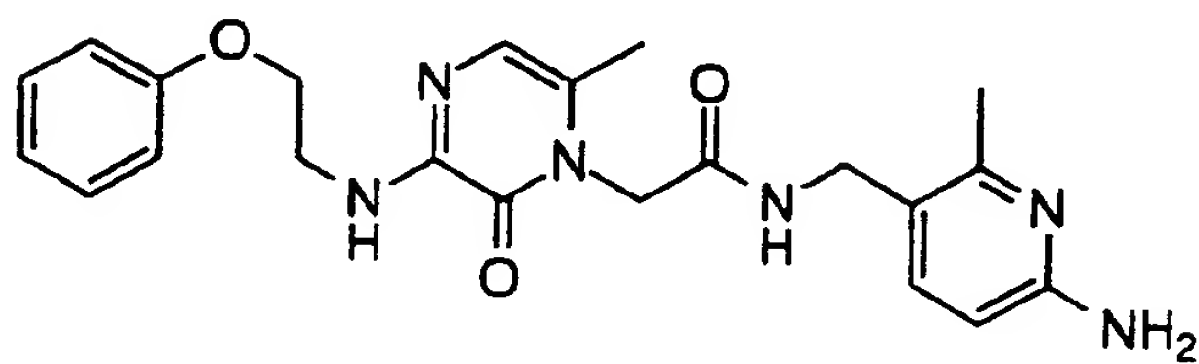
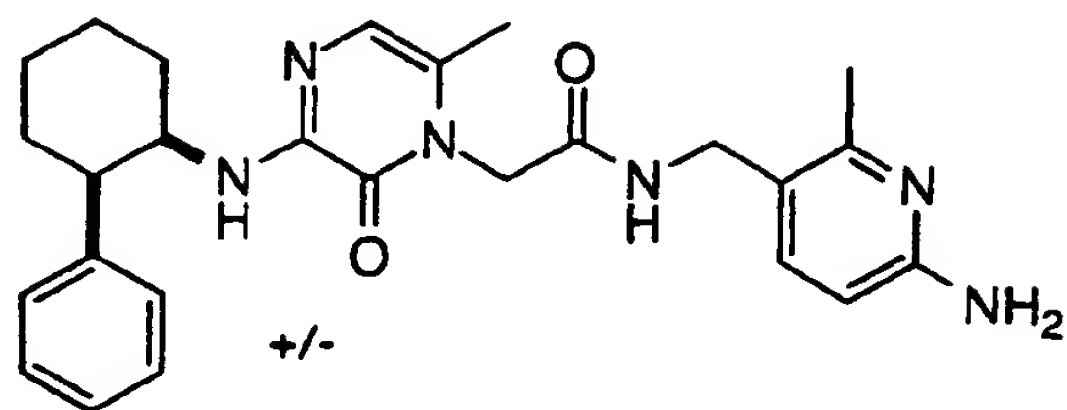
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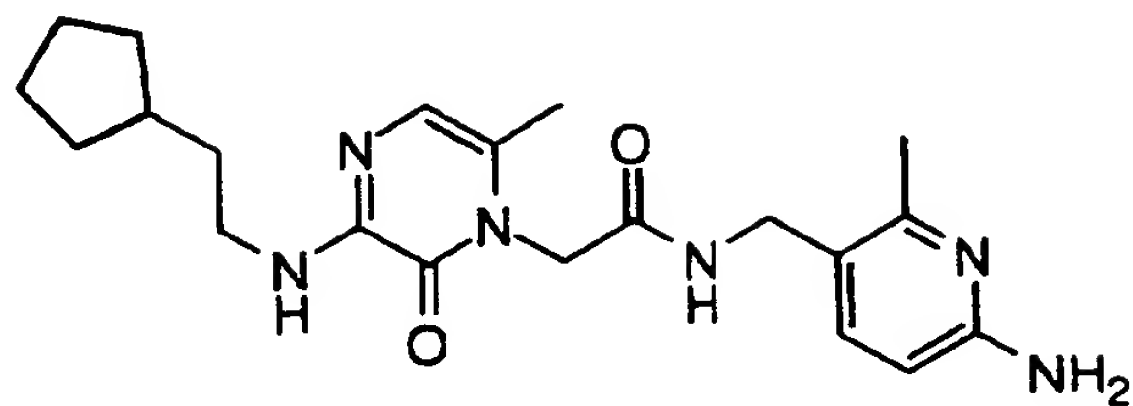
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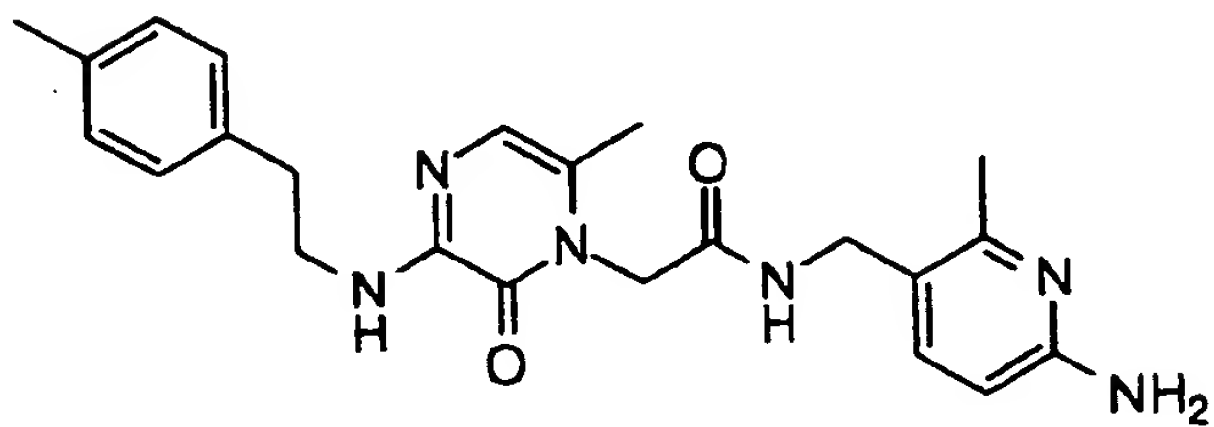
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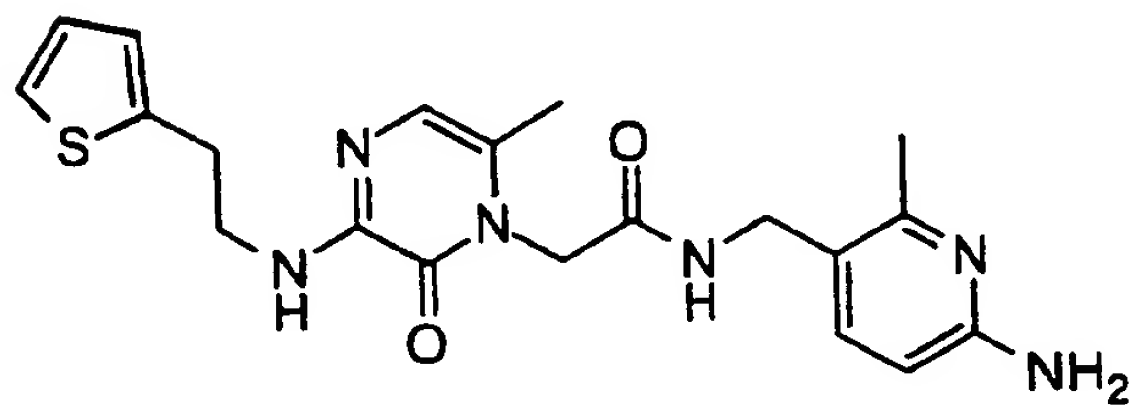
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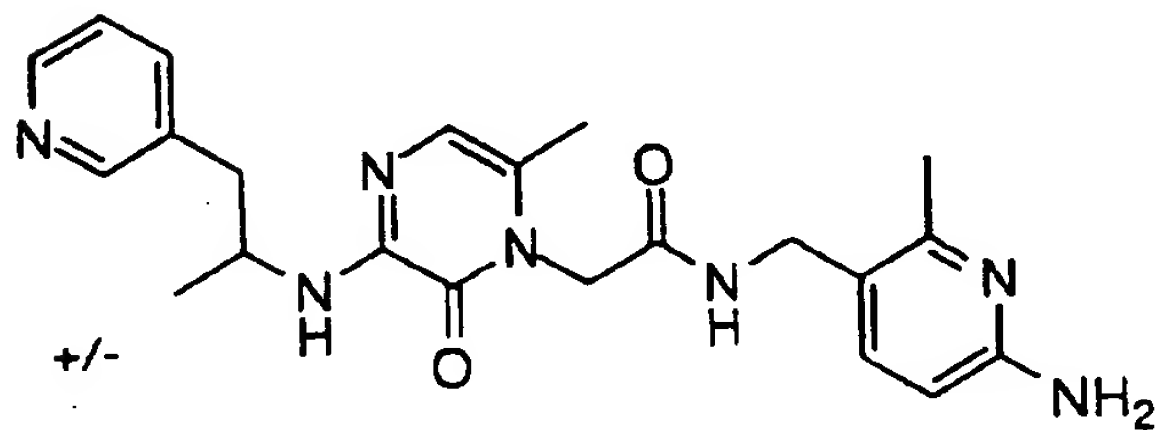
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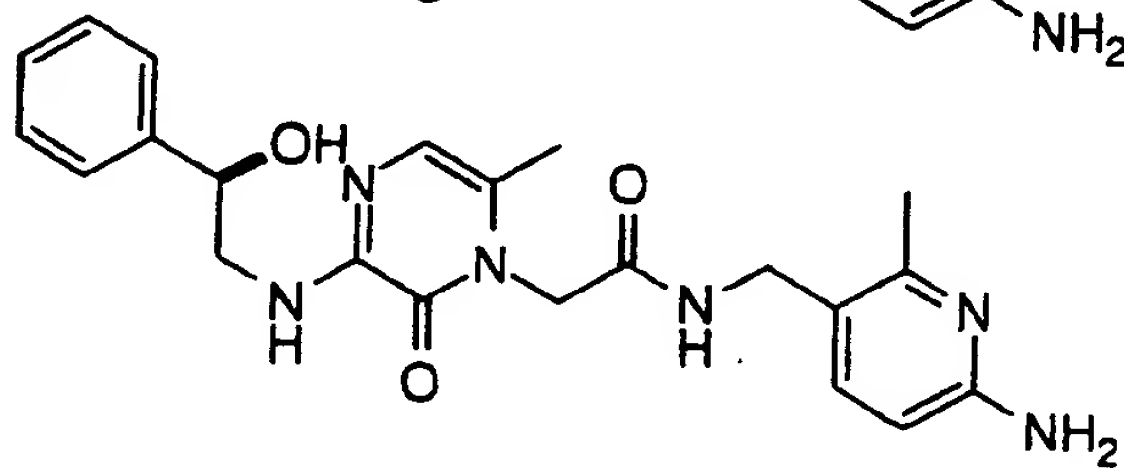
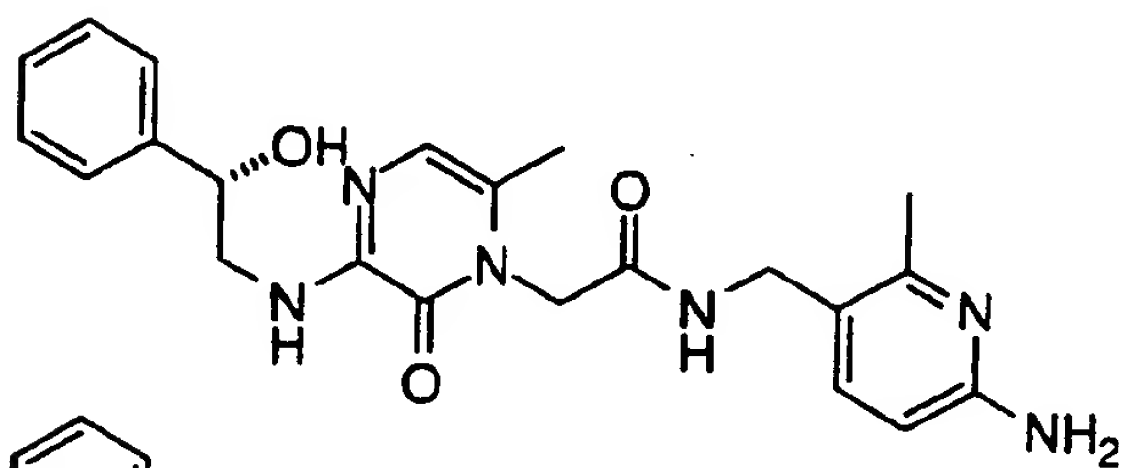
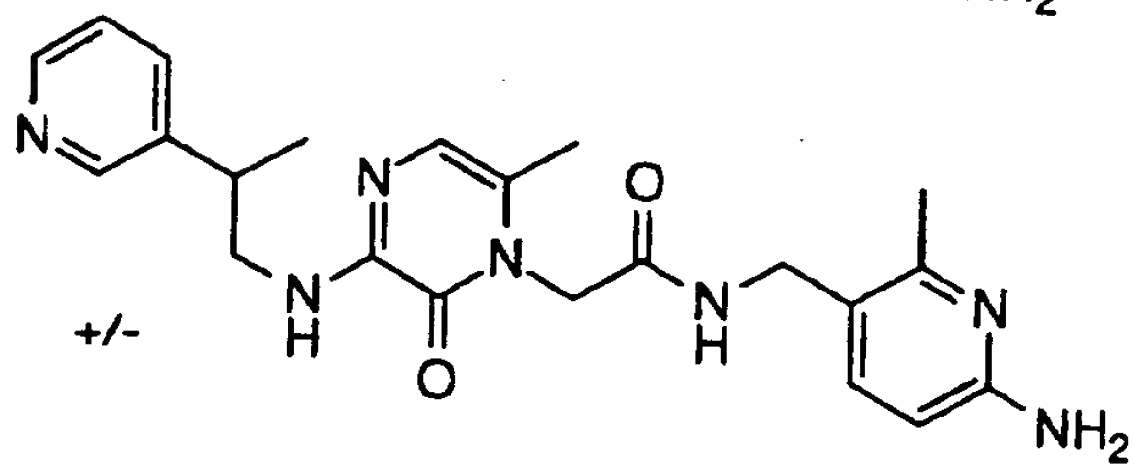
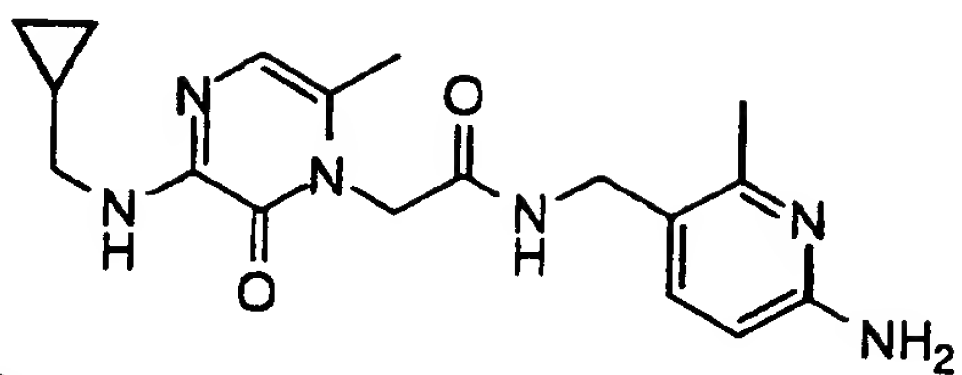


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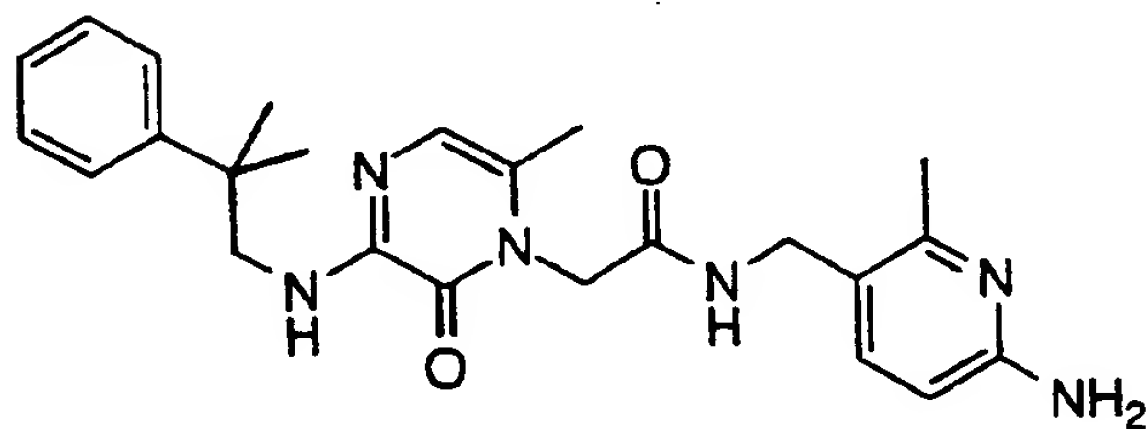
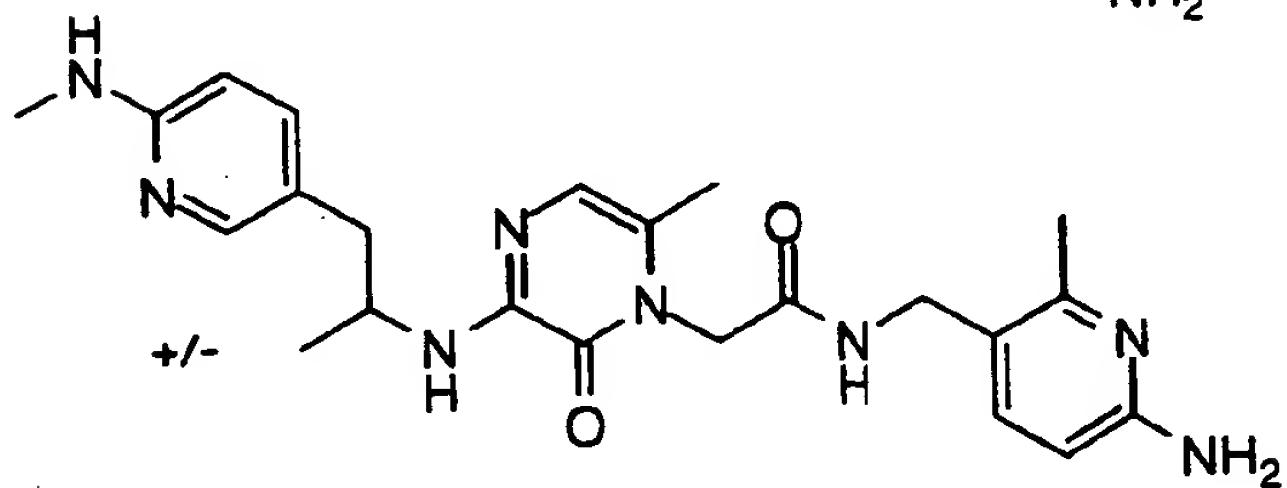
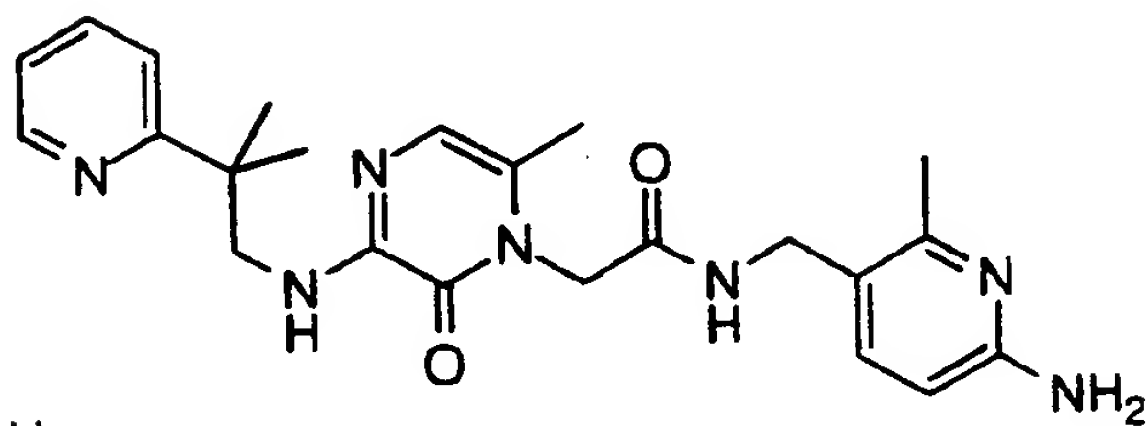
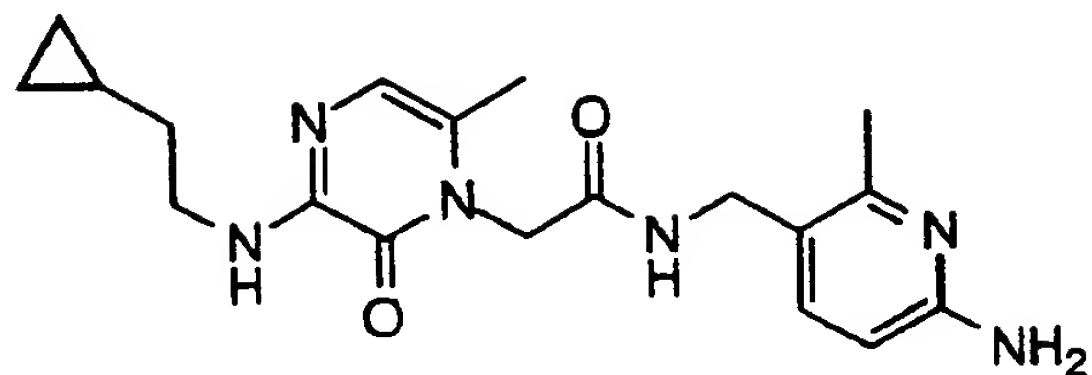


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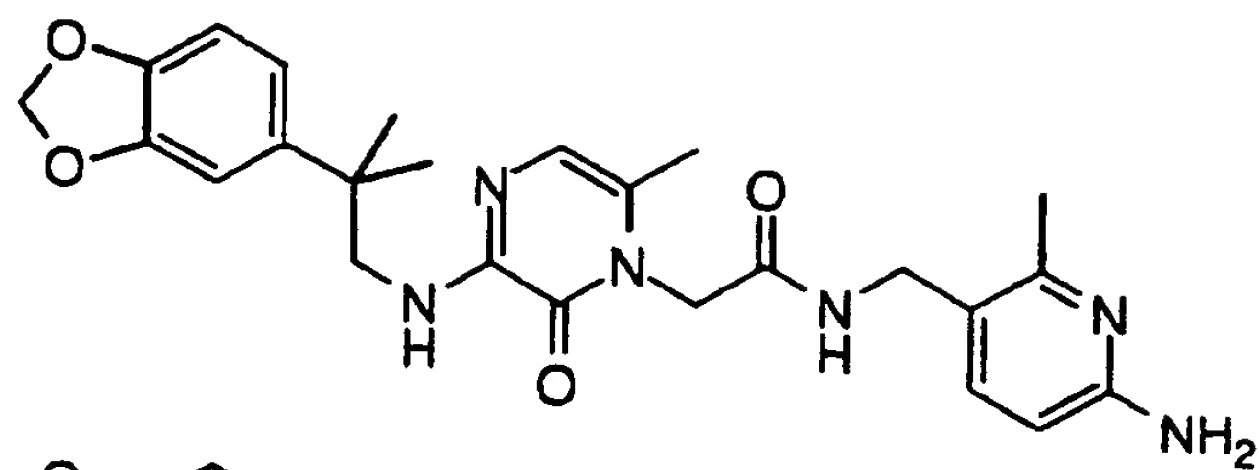
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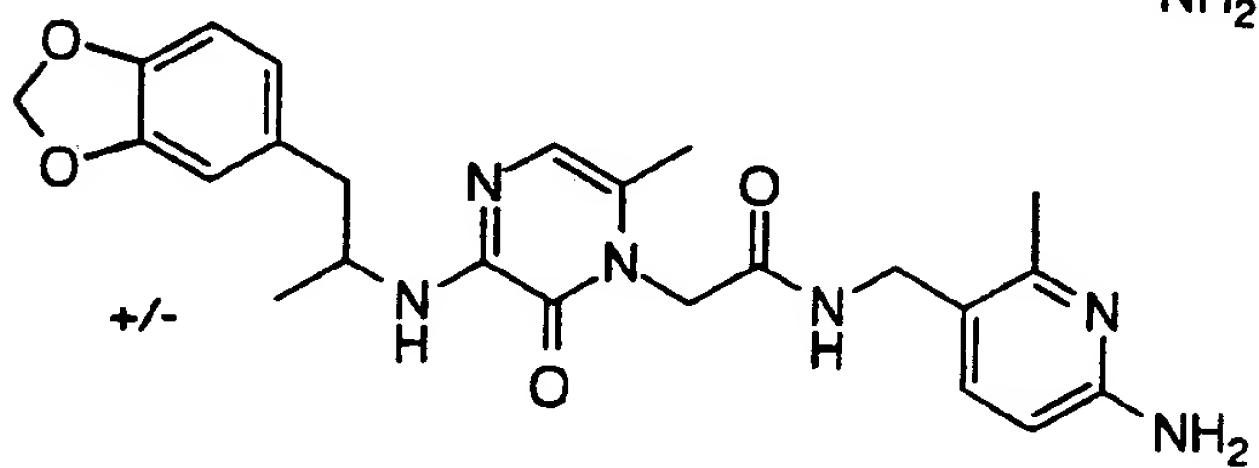
- 128 -



- 129 -

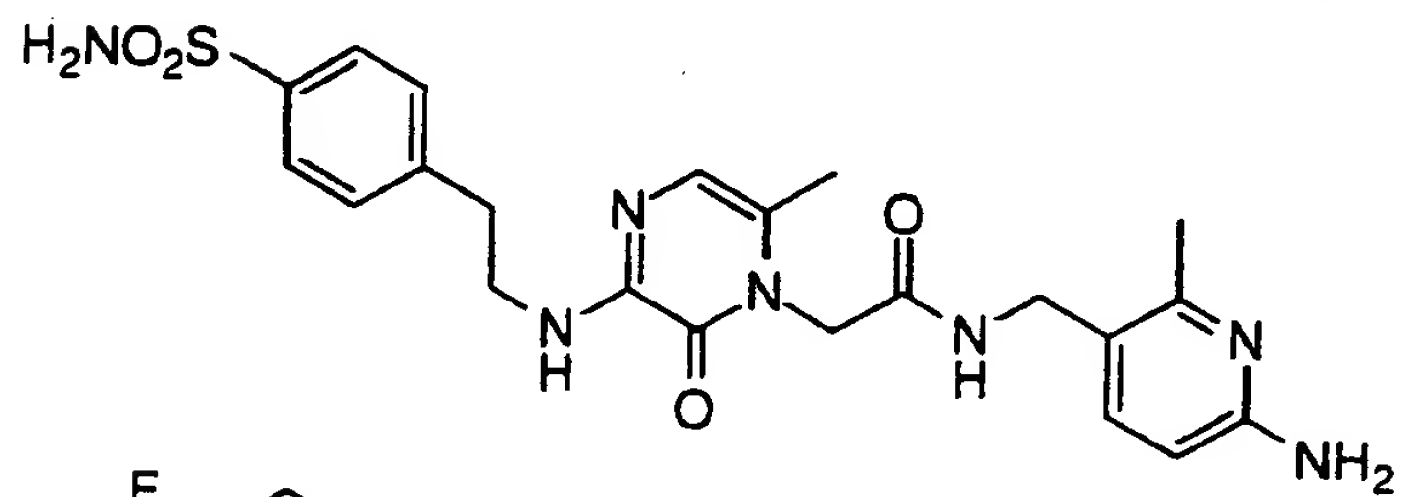


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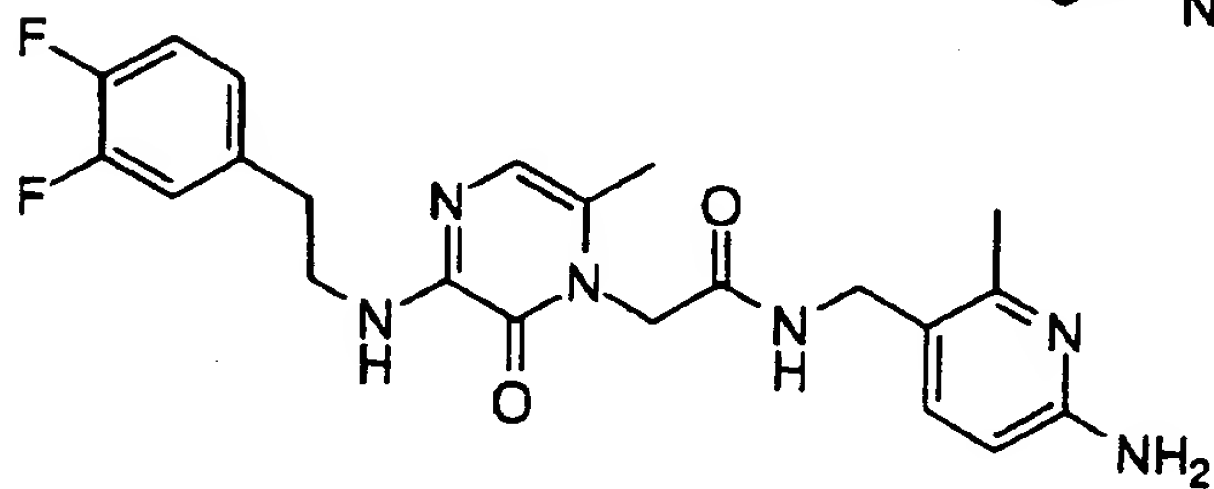


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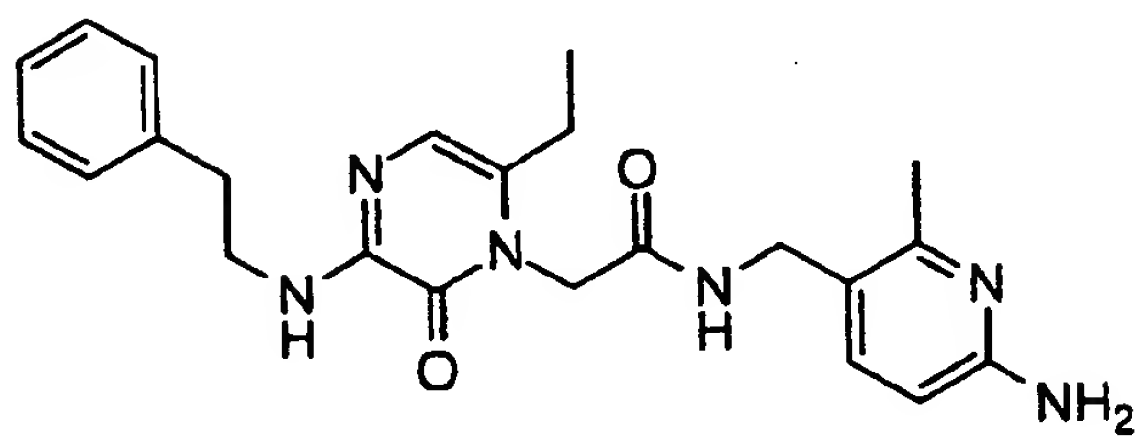
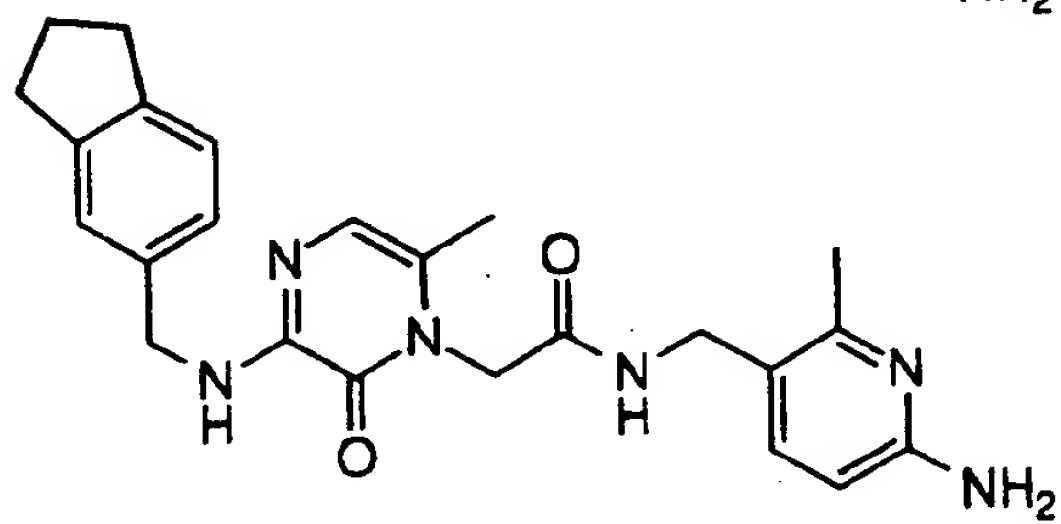
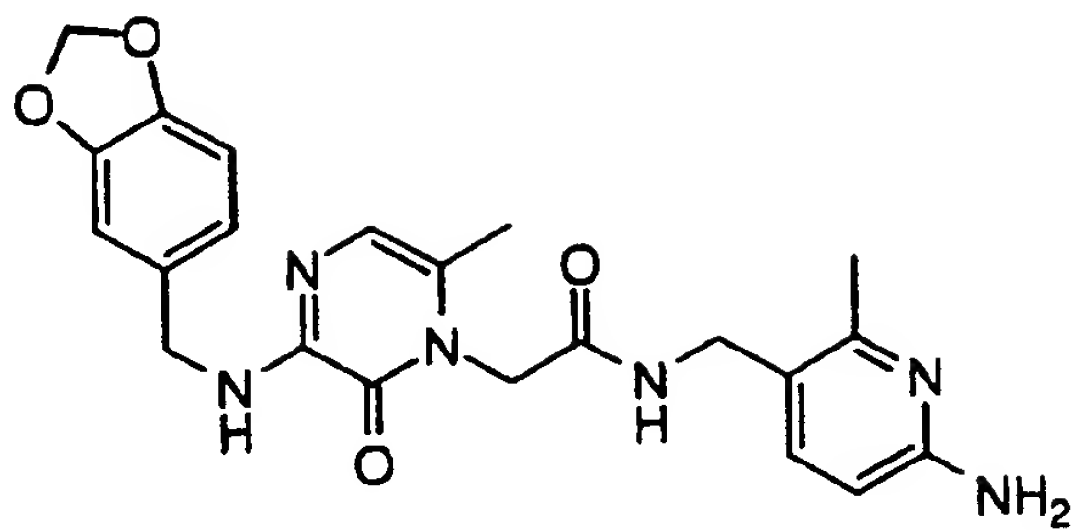


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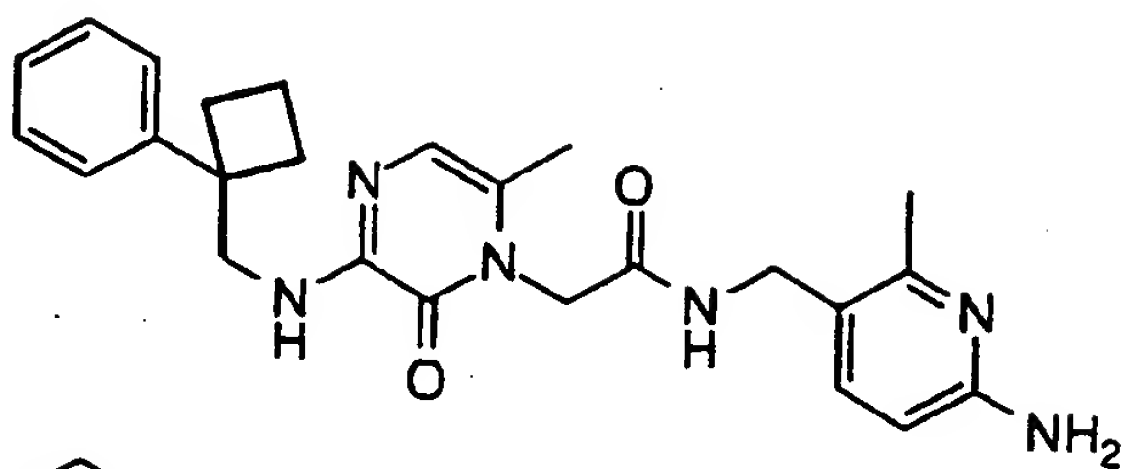


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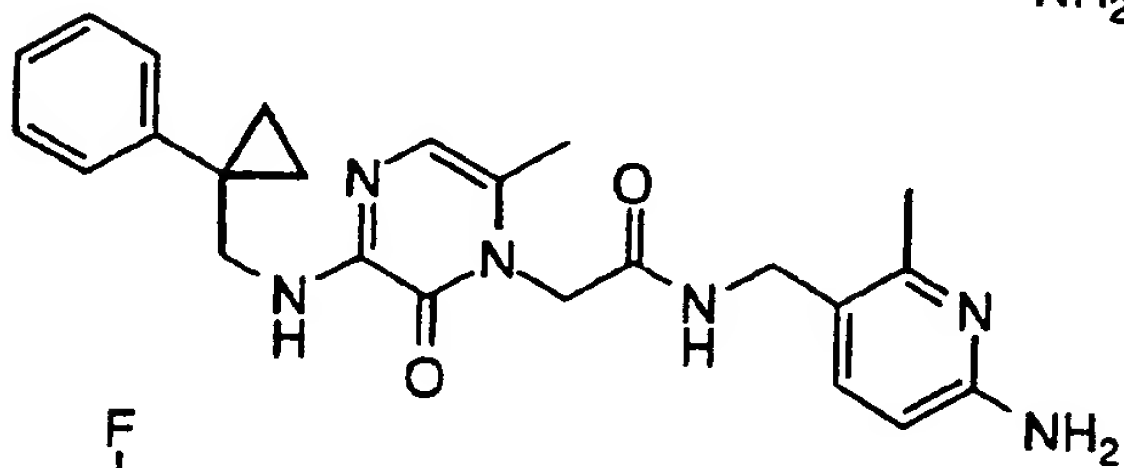
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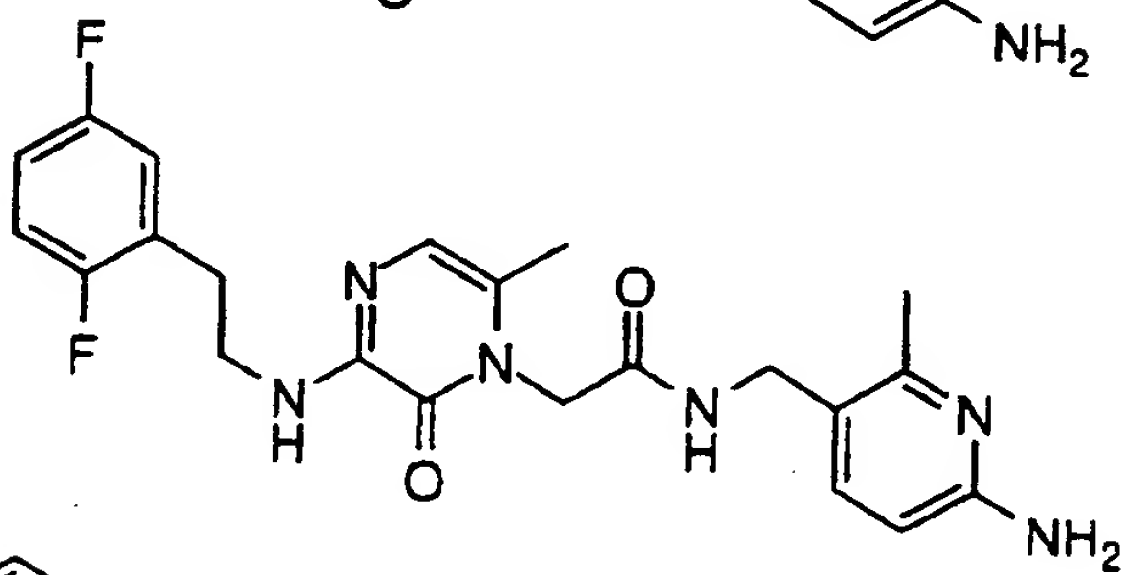
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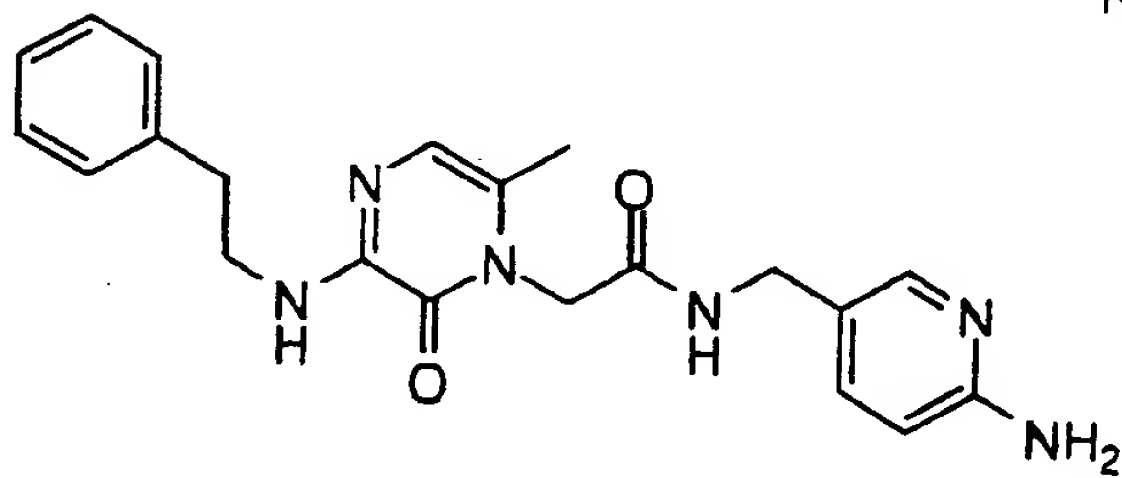
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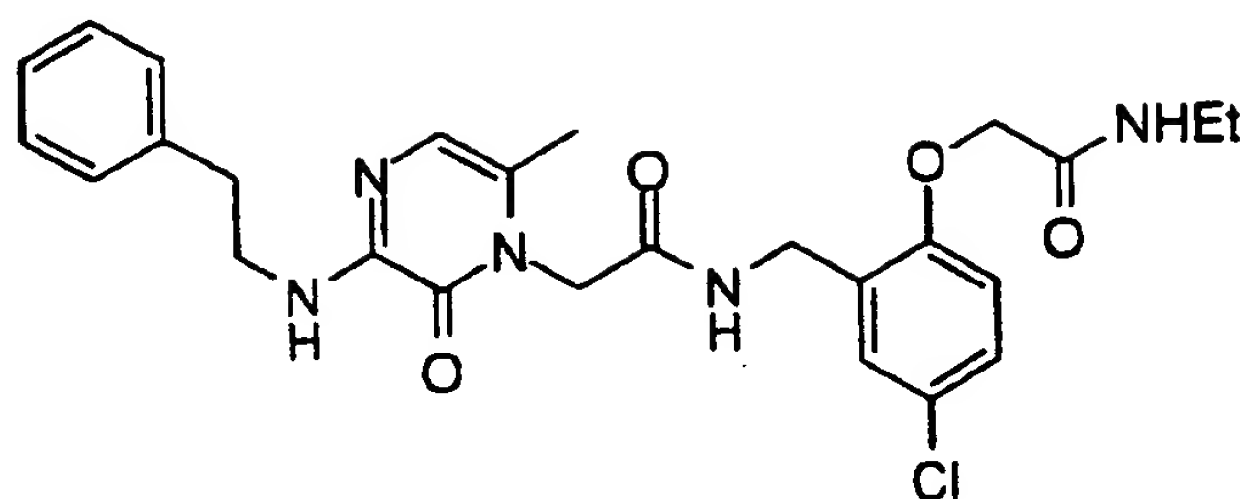


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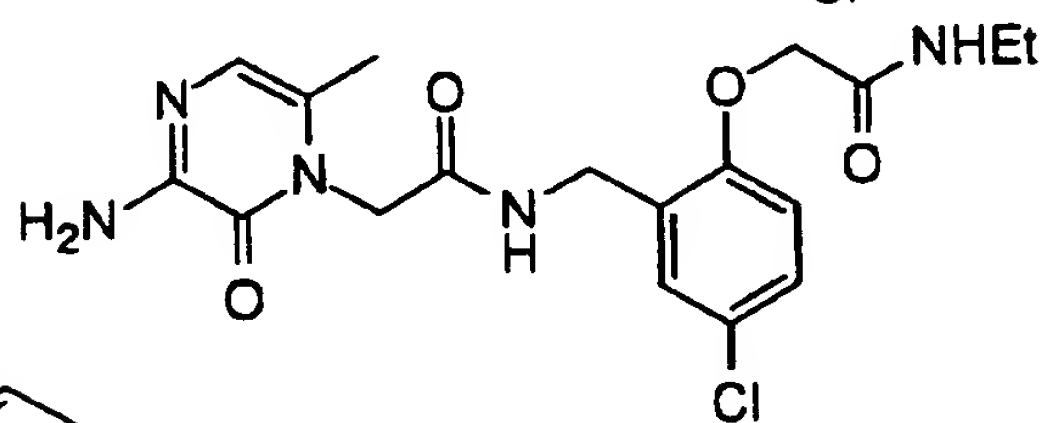


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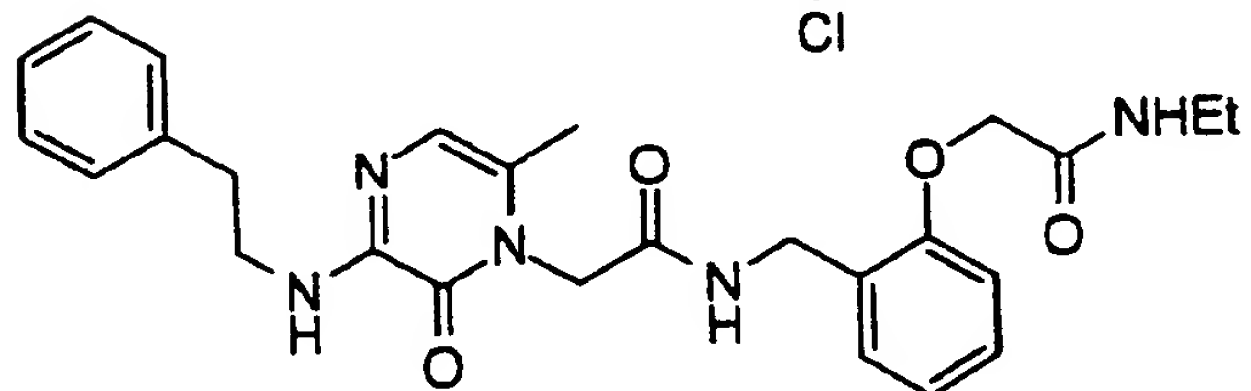
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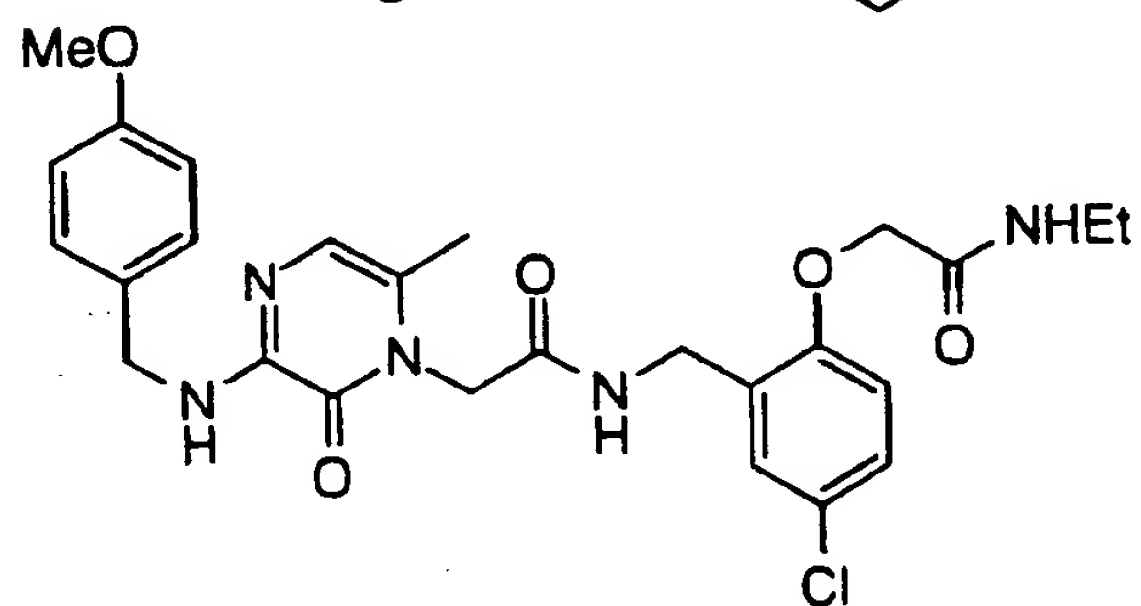
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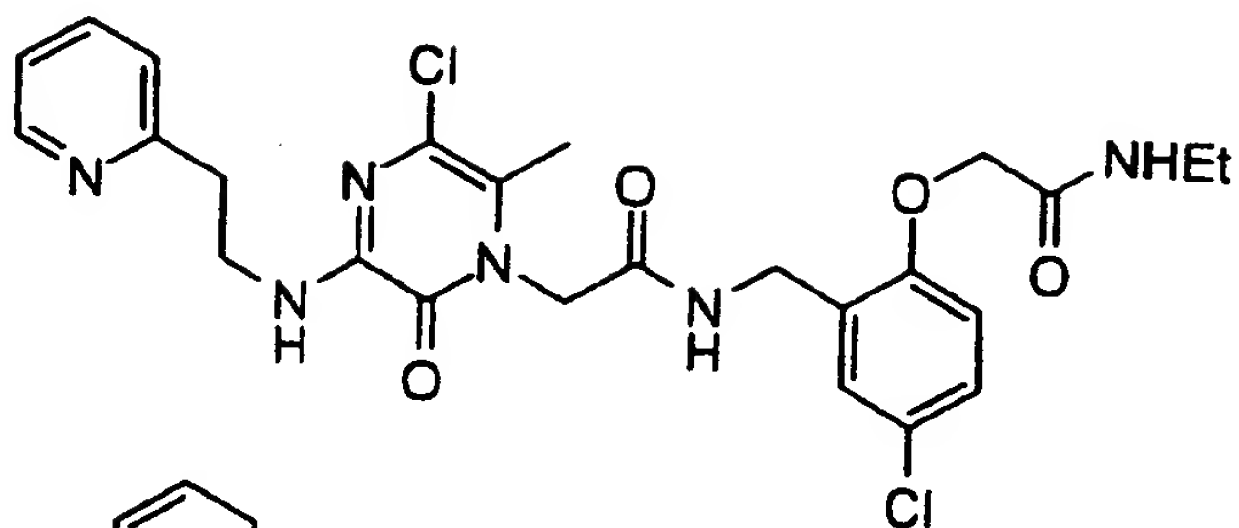


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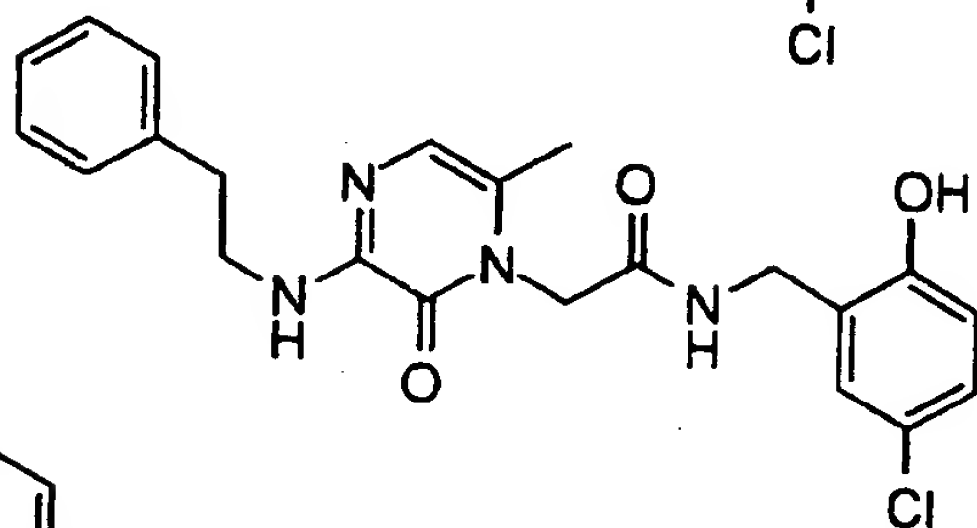


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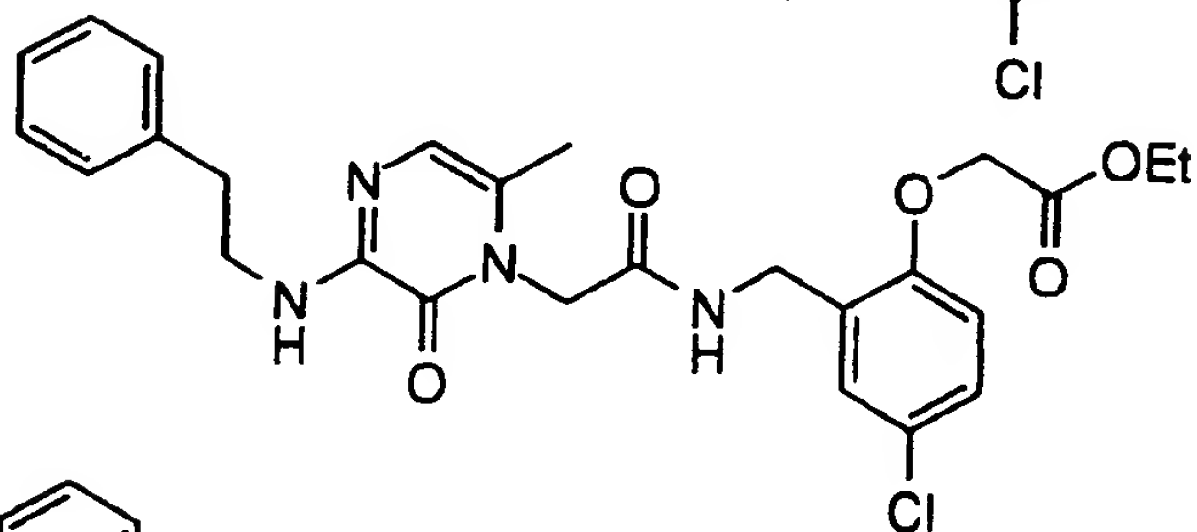
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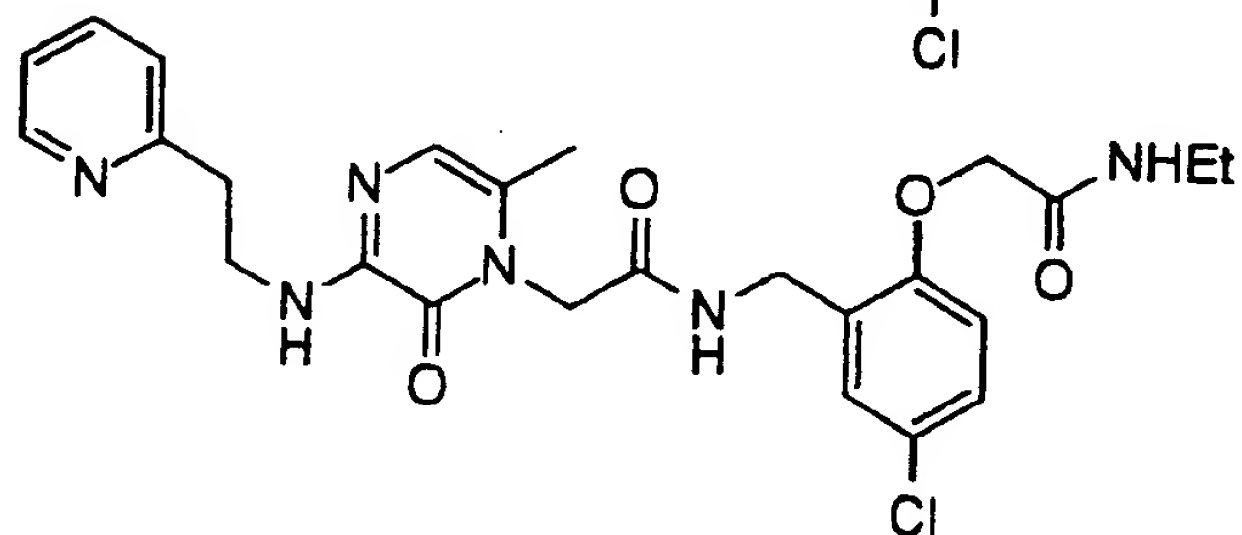
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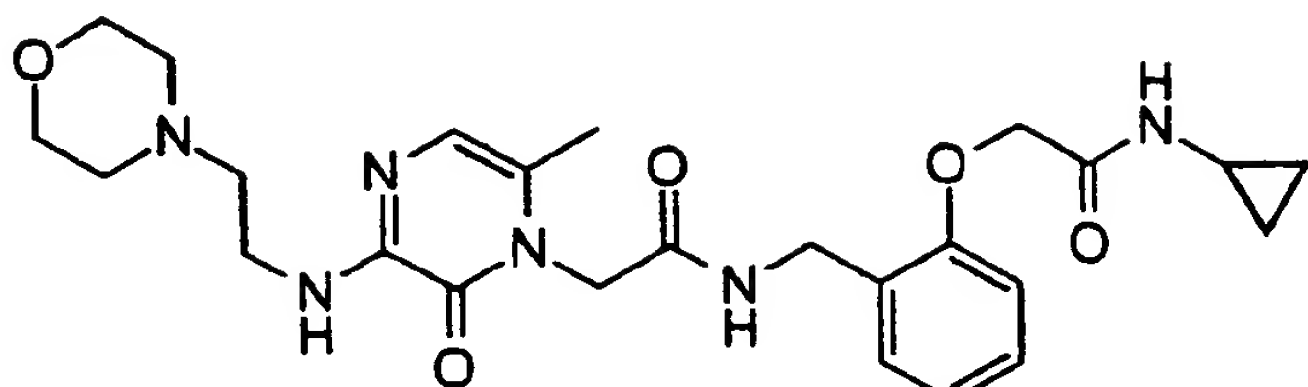


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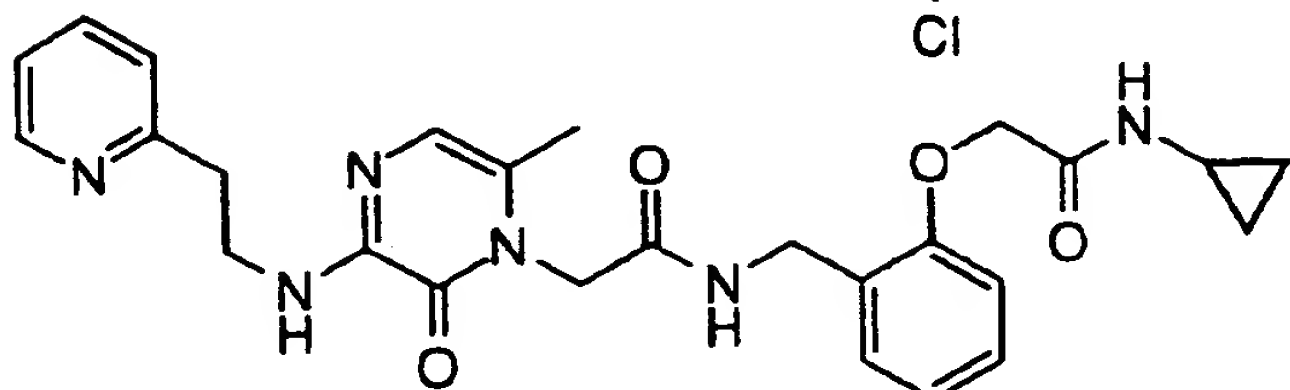


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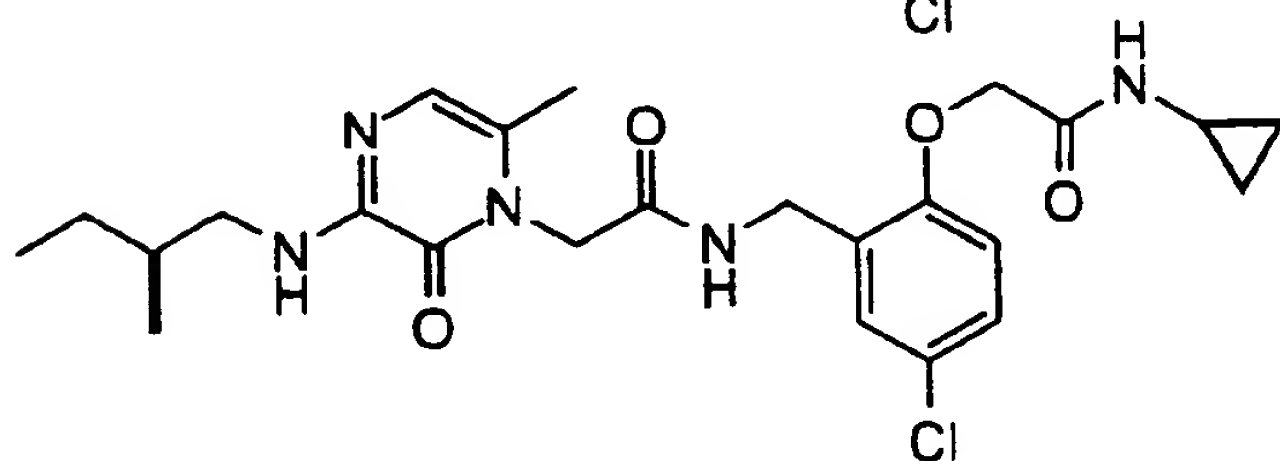
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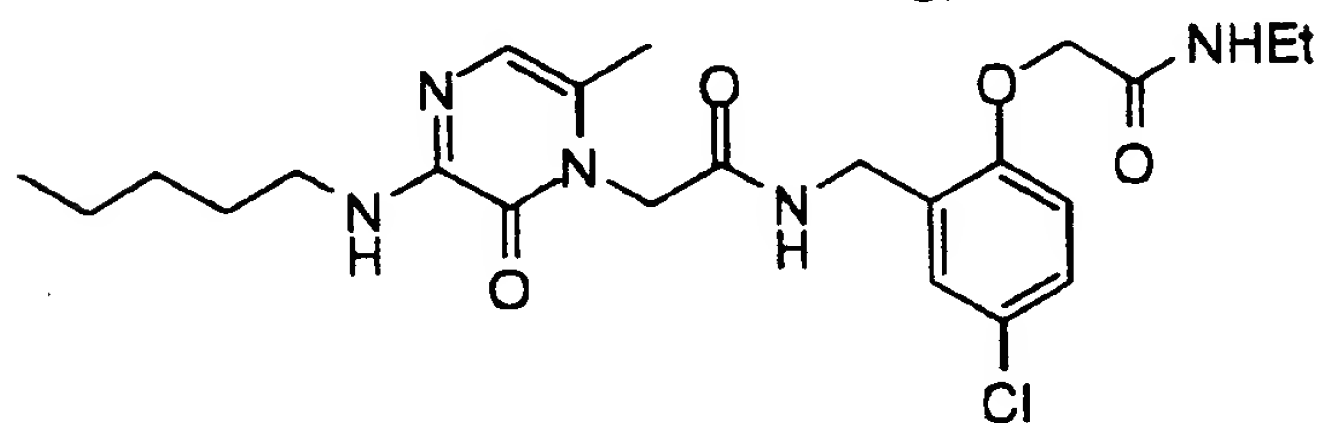
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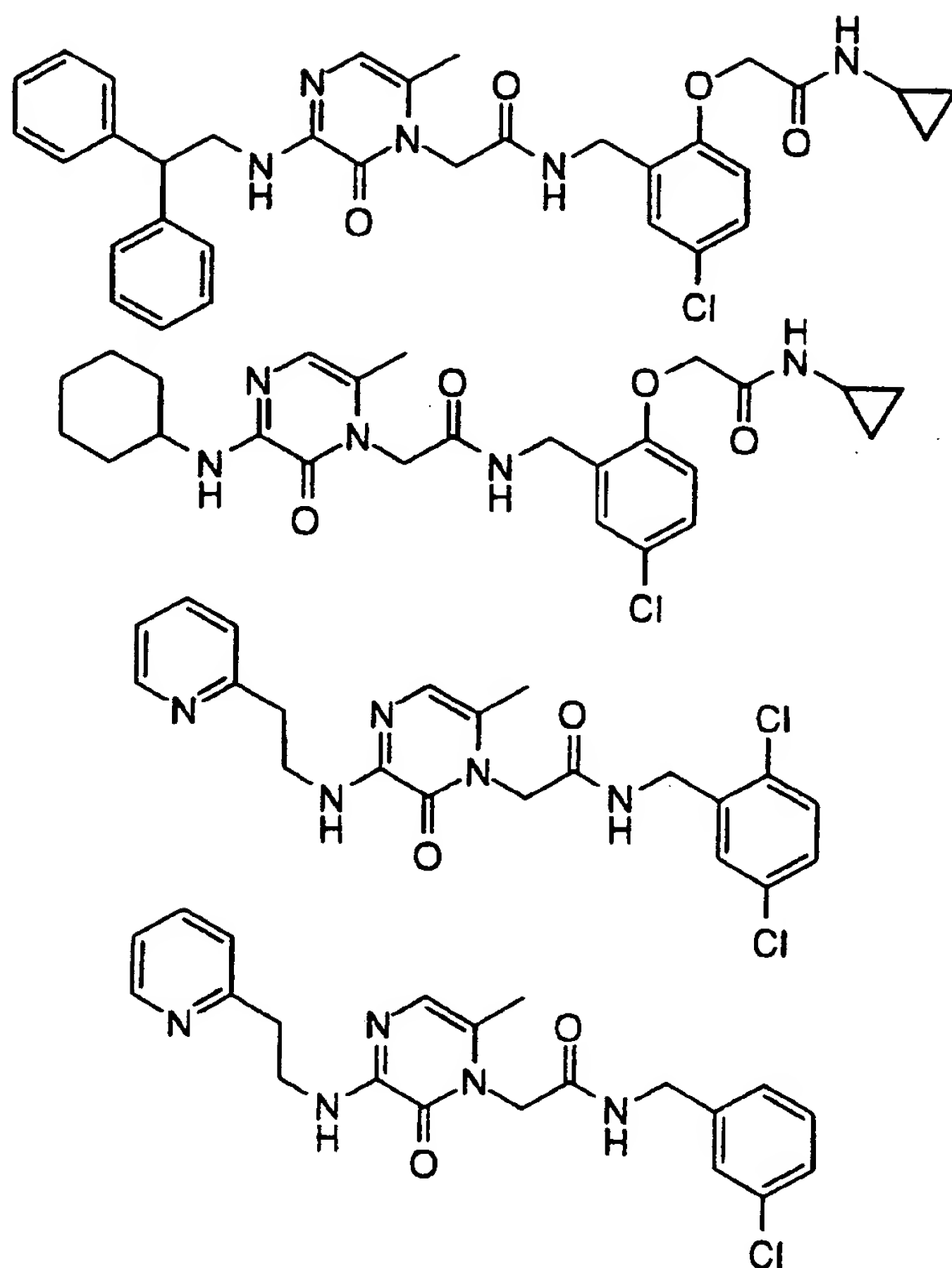


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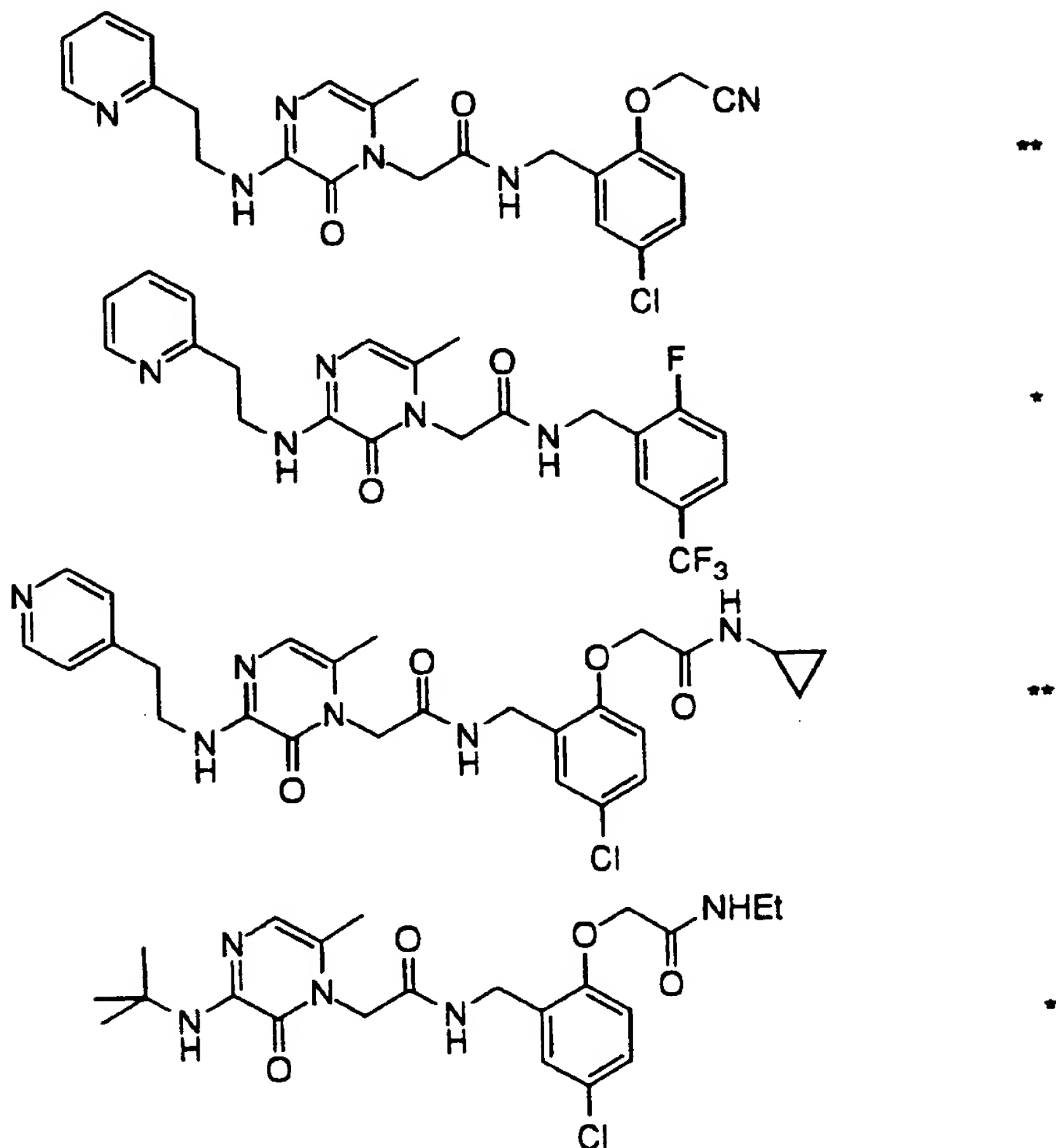


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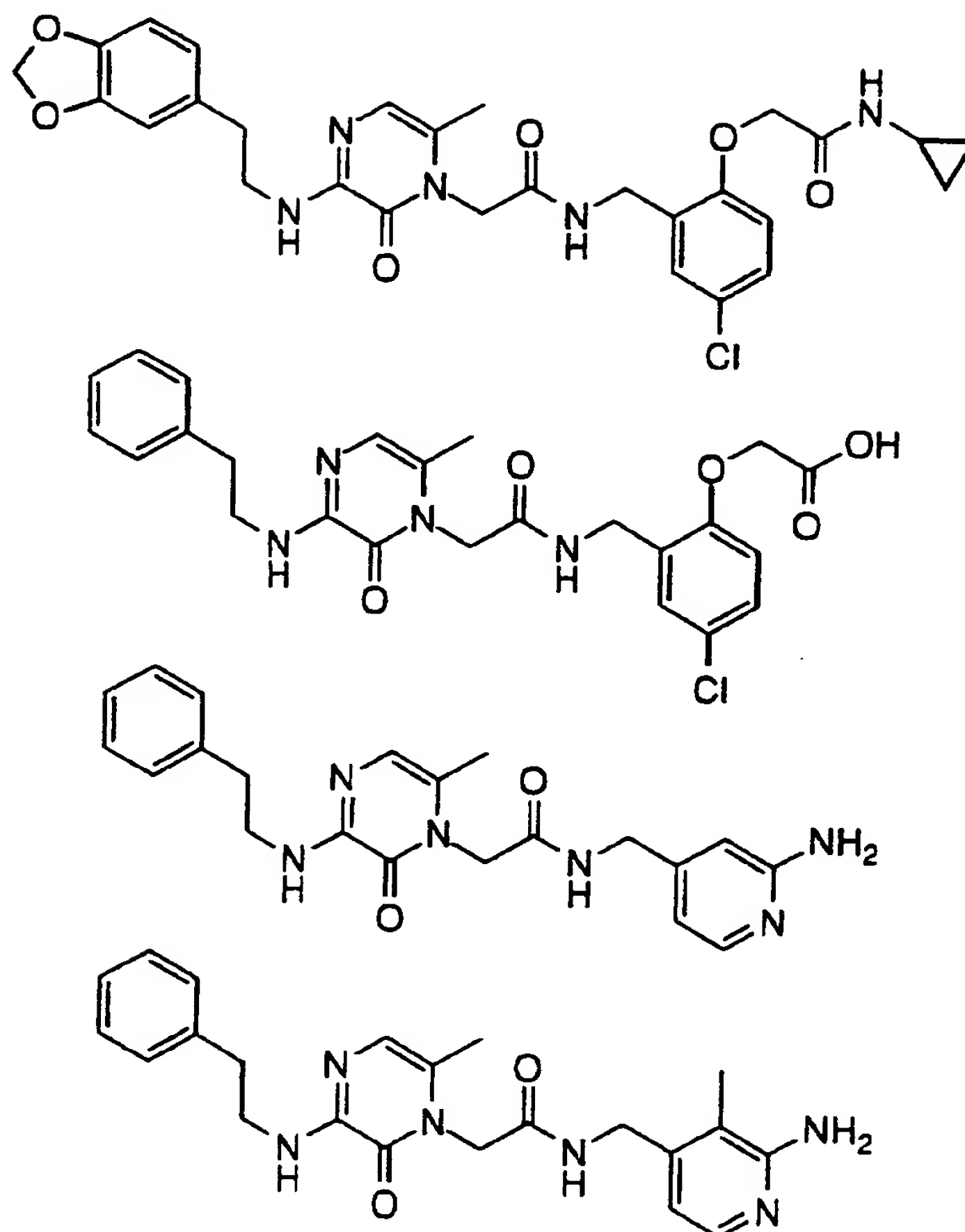
- 135 -



- 136 -



- 137 -

EXAMPLE LXXXIII5 *In Vivo* Studies To Measure Thrombotic Occlusions

Studies of 3-(2-Phenylethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone using the following rat ferric chloride assay substantially as described in *Thrombosis Research*, No. 60, page 269(1990) by Kurtz *et al* were used

10 to determine *in vivo* activity of the thrombin inhibitors of the invention. Male Sprague-Dawley rats (body weights 200-350 grams) were anesthetized with dial-urethane solution (0.1 ml/100 gm body weight i.p.), and a lateral tail vein was cannulated with a 23 gauge needle

- 138 -

connected to a 12 inch length of PE50 tubing. The tubing was attached to a 3-way valve by a tubing adapter. Saline (control) or test compound, as appropriate, was administered via the tail vein catheter. A tracheostomy was performed with a 0.75 inch length of PE205 tubing. The right carotid artery is exposed and a 1.3 mm diameter Doppler flow probe was placed on the vessel. Body temperature was maintained at 37°C using a heat lamp.

6 rats were randomized to continuous intravenous infusions of saline or test compound administered via the tail vein. Test compound was administered at a rate of 10 µg/kg/min. Treatment infusions were initiated 60 min before the placement of a 3 mm square piece of Whatman No. 1 filter paper saturated with 35% FeCl₃ onto the exposed carotid artery distal to the flow probe. Treatment infusions were continued for an additional 90 minutes after the application of FeCl₃ (total infusion duration 150 minutes) if thrombotic occlusions did not occur, or were terminated 30 minutes after thrombotic occlusion of the vessel. Time to occlusion was defined as the time from application of FeCl₃ to thrombotic occlusion of the vessel. At the termination of the study (90 minutes after application of FeCl₃ in animals which did not occlude, or at 30 minutes after thrombotic occlusion), 3 ml blood samples were drawn by cardiac puncture into 0.3 ml of 3.8% sodium citrate.

The results of the study showed that the tested compound was fully efficacious. None of the rats treated with the test compound showed evidence of thrombotic occlusion.

EXAMPLE LXXXIV

Tablet Preparation

Tablets containing 25.0, 50.0, and 100.0 mg., respectively, of the following active compounds are prepared as illustrated below (compositions A-I):

3-(2-Phenylethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (Active I),

- 139 -

3-(2-Phenethylamino)-6-methyl-1-[ethyl-(2-methylene-carboxamidomethyl-4-chlorophenoxy)-acetamido]-2-pyrazinone (Active II), and

- 5 3-Amino-6-methyl-1-[ethyl-(2-methylene-carboxamidomethyl-4-chlorophenoxy)-acetamido]-2-pyrazinone (Active III).

TABLE FOR DOSES CONTAINING FROM
25-100MG OF THE ACTIVE COMPOUND

10	<u>Component</u>	<u>Amount-mg</u>								
		<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>	<u>E</u>	<u>F</u>	<u>G</u>	<u>H</u>	<u>I</u>
	Active I	25	50	100	-	-	-	-	-	-
15	Active II	-	-	-	25	50	100	-	-	-
	Active III	-	-	-	-	-	-	25	50	100
20	Microcrystalline									
	cellulose	37.25	100	200	37.25	100	200	37.25	100	200
	Modified food									
	corn starch	37.25	4.25	8.5	37.25	4.25	8.5	37.25	4.25	8.5
25	Magnesium									
	stearate	0.5	0.75	1.5	0.5	0.75	1.5	0.5	0.75	1.5

30 All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 25.0, 50.0, and 100.0 mg, respectively, of active ingredient per tablet.

- 140 -

EXAMPLE LXXXVTablet Preparation

Exemplary compositions of 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride Type A monohydrate (Active IV) tablets are shown below:

Component	0.25 mg	2 mg	10 mg	50 mg
Active IV	0.500%	1.000%	5.000%	14.29%
mannitol	49.50%	49.25%	47.25%	42.61%
microcrystalline cellulose	49.50%	49.25%	47.25%	42.61%
magnesium stearate	0.500%	0.500%	0.500%	0.500%

2, 10 and 50 mg tablets were film-coated with an aqueous dispersion of hydroxypropyl cellulose, hydroxypropyl methylcellulose and titanium dioxide, providing a nominal weight gain of 2.4%.

Tablet preparation via direct compression

Active IV, mannitol and microcrystalline cellulose were sieved through mesh screens of specified size (generally 250 to 750 μ m) and combined in a suitable blender. The mixture was subsequently blended (typically 15 to 30 min) until the drug was uniformly distributed in the resulting dry powder blend. Magnesium stearate was screened and added to the blender, after which a precompression tablet blend was achieved upon additional mixing (typically 2 to 10 min). The precompression tablet blend was then compacted under an applied force, typically ranging from 0.5 to 2.5 metric tons, sufficient to yield tablets of suitable physical strength with acceptable disintegration times (specifications will vary with the size and potency of the compressed tablet). In the case of the 2, 10 and 50 mg potencies, the tablets were dedusted and film-coated with an aqueous dispersion of water-soluble polymers and pigment.

- 141 -

Tablet preparation via dry granulation

Alternatively, a dry powder blend is compacted under modest forces and remilled to afford granules of specified particle size. The granules are then mixed with magnesium stearate and tableted as stated above.

EXAMPLE LXXXVIIntravenous Formulations

Intravenous formulations of 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride Type A monohydrate (Active IV) were prepared according to general intravenous formulation procedures.

15	<u>Component</u>	<u>Estimated range</u>
	Active IV	0.12 - 0.61 mg
	D-glucuronic acid*	0.5 - 5 mg
20	Mannitol NF	50-53 mg
	1 N Sodium Hydroxide	q.s. pH 3.9 - 4.1
25	Water for injection	q.s. 1.0 mL

Exemplary compositions A-C are as follows:

30	<u>Component</u>	<u>A</u>	<u>B</u>	<u>C</u>
	Active IV	0.61 mg*	0.30**	0.15***
	D-glucuronic acid*	1.94 mg	1.94 mg	1.94 mg
35	Mannitol NF	51.2 mg	51.2 mg	51.2 mg
	1 N Sodium Hydroxide	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0
	Water for injection	q.s. 1.0 mL	q.s. 1.0 mL	q.s. 1.0 mL

- 142 -

- * 0.50 mg free base
- ** 0.25 mg free base
- *** 0.12 mg free base

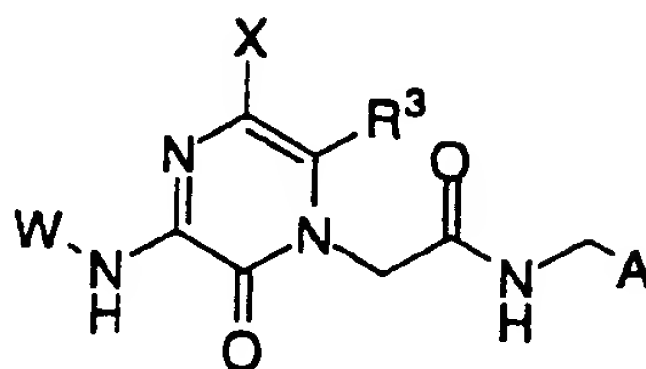
5 Various other buffer acids, such as L-lactic acid, acetic acid, citric acid or any pharmaceutically acceptable acid/conjugate base with reasonable buffering capacity in the pH range acceptable for intravenous administration may be substituted for glucuronic acid.

10

- 143 -

WHAT IS CLAIMED IS:

1. A compound having the formula:



- 5 wherein
W is

hydrogen,
R¹,
10 R¹OCO,
R¹CO,
R¹(CH₂)_nNHCO, or
(R¹)₂CH(CH₂)_nNHCO,
wherein n is 0-4;

- 15 R¹ is

R²,
R²(CH₂)_mC(R¹²)₂, where m is 0-3, and each R¹² can be the same
or different,
20 (R²)(OR²)CH(CH₂)_p, where p is 1-4,
R²C(R¹²)₂(CH₂)_m, wherein m is 0-3, and each R¹² can be the
same or different, wherein (R¹²)₂ can also form a ring with
C represented by C₃-7 cycloalkyl,
R²CH₂C(R¹²)₂(CH₂)_q, wherein m is 0-2, and each R¹² can be the
25 same or different, wherein (R¹²)₂ can also form a ring with
C represented by C₃-7 cycloalkyl,
(R²)₂CH(CH₂)_r, where r is 0-4 and each R² can be the same or
different, and wherein (R²)₂ can also form a ring with CH
represented by C₃-7 cycloalkyl, C₇-12 bicyclic alkyl, C₁₀-16

- 144 -

- tricyclic alkyl, or a 5- to 7- membered mono- or bicyclic heterocyclic ring which can be saturated or unsaturated, and which contains from one to three heteroatoms selected from the group consisting of N, O and S,
- 5 $R^2O(CH_2)_p$, wherein p is 1-4, or
 $R^2(COOR^3)(CH_2)_r$, where r is 1-4;
- R^2 and R^{14} are independently
- 10 phenyl, unsubstituted or substituted with one or more of C₁-4 alkyl, C₁-4 alkoxy, halogen, hydroxy, COOH, CONH₂, or SO₂NH₂,
- naphthyl,
biphenyl,
a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
- 15 heterocyclic ring or non-heterocyclic ring which can be saturated or unsaturated, wherein the heterocyclic ring contains from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the heterocyclic or non-heterocyclic ring is unsubstituted or substituted with halogen or hydroxy,
- 20 C₁-7 alkyl, unsubstituted or substituted with one or more of hydroxy,
COOH,
amino,
aryl,
- 25 C₃-7 cycloalkyl,
CF₃,
N(CH₃)₂,
-C₁-3alkylaryl,
heteroaryl, or
- 30 heterocycloalkyl,
CF₃
C₃-7 cycloalkyl, unsubstituted or substituted with aryl,
C₇-12 bicyclic alkyl, or
C₁₀-16 tricyclic alkyl;

- 145 -

R³ is

hydrogen,
C1-4 alkyl,
C3-7 cycloalkyl, or
trifluoromethyl;

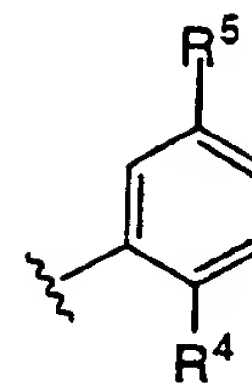
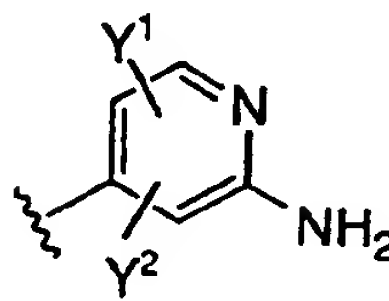
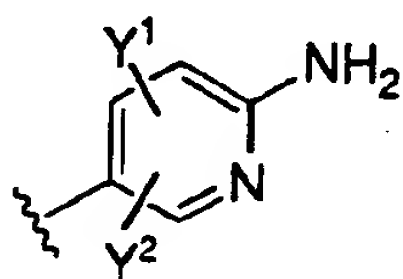
5

X is

hydrogen, or
halogen;

10

A is chosen from one of the following radicals:



wherein Y¹ and Y² are independently
hydrogen,
C1-4 alkyl,
C1-4 alkoxy,
C3-7 cycloalkyl,
halogen, or
trifluoromethyl;

15

20

R⁴ is

hydrogen,
C1-4 alkyl,
C1-4 alkoxy,
halogen,
-OCH₂CF₃,
-OCH₂CN,
-COOH,
-OH,

25

- 146 -

- COOR⁶, where R⁶ is C₁₋₄alkyl,
-CONR⁷R⁸, where R⁷ and R⁸ are independently
hydrogen or C₁₋₄alkyl,
-(CH₂)₁₋₄OH,
5 -CH₂NHC(O)CH₃,
-CH₂NHC(O)CF₃,
-CH₂NHSO₂CH₃,
-SO₂NH₂,
-(CH₂)₁₋₄SO₂NR⁷R⁸,
10 -(CH₂)₁₋₄SO₂R⁶,
a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
heterocyclic ring which can be saturated or unsaturated, and
which contains from one to four heteroatoms selected from the
group consisting of N, O and S,
15 -ZCH₂CO₂H,
-ZCH₂CO₂CH₃,
-ZCH₂R¹⁴,
-ZCH₂CO₂(CH₂)₁₋₃CH₃,
-Z(CHR⁹)₁₋₃C(O)NR¹⁰R¹¹,
20 wherein
R⁹ is H or C₁₋₄ alkyl,
R¹⁰ and R¹¹ are independently
hydrogen,
C₃₋₇ cycloalkyl,
25 aryl,
heteroaryl,
heterocycloalkyl,
-(CH₂)₁₋₂NCH₂CH₃,
C₁₋₄ alkyl unsubstituted or substituted with one or more
30 of:
hydroxy,
COOH,
amino,
aryl,

- 147 -

heteroaryl, or
heterocycloalkyl, or
R¹⁰ and R¹¹ are joined to form a four to seven
membered cycloalkyl ring unsubstituted or
substituted with hydroxy, amino or aryl,

5

wherein Z is O, S or CH₂;

R⁵ is

10

hydrogen,
halogen,
C₁-4 alkyl,
C₁-4 alkoxy,
CF₃,
CN, or
CO₂NH₂; and

15

R¹² is

20

hydrogen,
phenyl, unsubstituted or substituted with one or more of C₁-4
alkyl, C₁-4 alkoxy, halogen, hydroxy, COOH, CONH₂,
naphthyl,
biphenyl,
a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
heterocyclic ring which can be saturated or unsaturated, and
- which contains from one to four heteroatoms selected from the
group consisting of N, O and S,

25

C₁-4 alkyl, unsubstituted or substituted with one or more of
hydroxy,
COOH,
amino,
aryl,
heteroaryl, or
heterocycloalkyl,

30

- 148 -

CF₃
 C₃-7 cycloalkyl,
 C₇-12 bicyclic alkyl, or
 C₁₀-16 tricyclic alkyl;

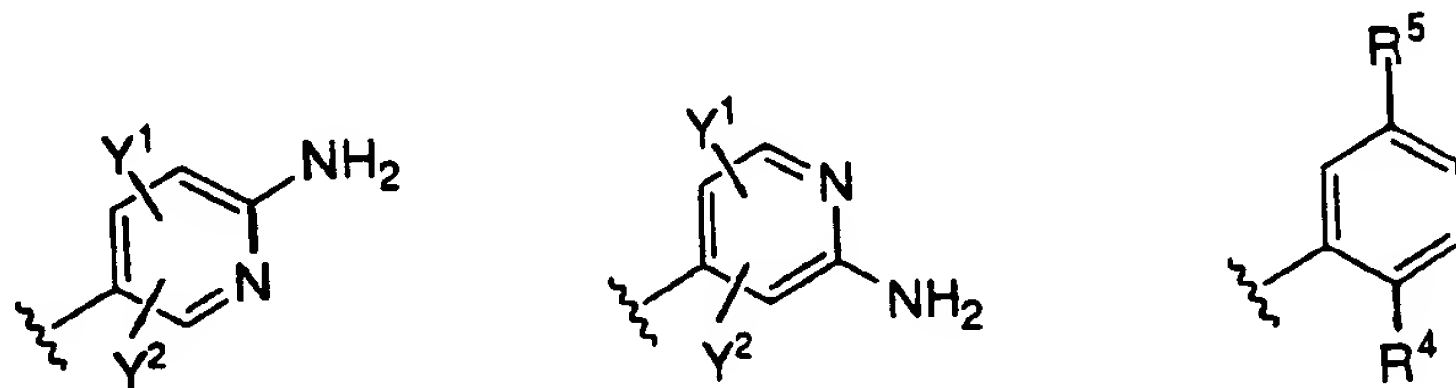
5

and pharmaceutically acceptable salts thereof.

2. A compound of Claim 1, and pharmaceutically acceptable salts thereof, wherein R³ is C₁-4 alkyl.

10

3. A compound of Claim 2, and pharmaceutically acceptable salts thereof, wherein A is chosen from one of the following radicals:



15

wherein Y¹ and Y² are independently hydrogen or C₁-4 alkyl;

R⁴ is

hydrogen,
 halogen,
 -OCH₂CN,
 -OH,
 -ZCH₂CO₂H, or
 -Z(CHR⁹)₁₋₃C(O)NR¹⁰R¹¹,

20

wherein

25

R⁹ is H or C₁-4 alkyl, and
 R¹⁰ and R¹¹ are independently
 hydrogen,
 C₃-7 cycloalkyl,
 -(CH₂)₁₋₂NCH₂CH₃, or

- 149 -

C₁₋₄ alkyl,wherein Z is O, S or CH₂;5 R⁵ ishydrogen,
halogen, or
CF₃.10 4. A compound of Claim 3, and pharmaceutically acceptable salts thereof, wherein W is hydrogen or R¹.

5. A compound of Claim 4, and pharmaceutically acceptable salts thereof, wherein

15

R¹ isR²,
R²(CH₂)_mC(R¹²)₂, where m is 0-3, and each R¹² can be the same or different,20 R²C(R¹²)₂(CH₂)_m, wherein m is 0-3, and each R¹² can be the same or different, wherein (R¹²)₂ can also form a ring with C represented by C₃₋₇ cycloalkyl,25 (R²)₂CH(CH₂)_r, where r is 0-4 and each R² can be the same or different, and wherein (R²)₂ can also form a ring with CH represented by C₃₋₇ cycloalkyl, C₇₋₁₂ bicyclic alkyl, C₁₀₋₁₆ tricyclic alkyl, or a 5- to 7- membered mono- or bicyclic heterocyclic ring which can be saturated or unsaturated, and which contains from one to three heteroatoms selected from the group consisting of N, O and S, or30 R²O(CH₂)_p, wherein p is 1-4;R² and R¹⁴ are independently
phenyl, unsubstituted or substituted with one or more of C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxy, or SO₂NH₂,

- 150 -

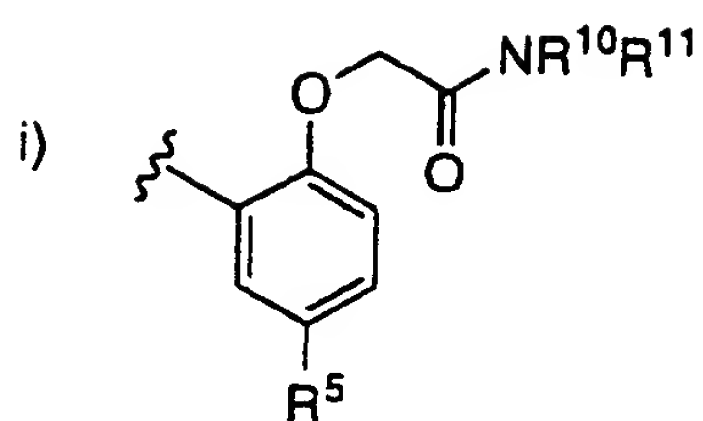
5 a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
heterocyclic ring or non-heterocyclic ring which can be saturated
or unsaturated, wherein the heterocyclic ring contains from one to
four heteroatoms selected from the group consisting of N, O and
S, and wherein the heterocyclic or non-heterocyclic ring is
unsubstituted or substituted with halogen or hydroxy,
C₁-7 alkyl, unsubstituted or substituted with one or more of
hydroxy,
COOH,
10 C₃-7 cycloalkyl,
CF₃,
N(CH₃)₂,
-C₁-3alkylaryl,
heteroaryl, or
15 heterocycloalkyl,
CF₃, or
C₃-7 cycloalkyl, unsubstituted or substituted with aryl; and

20 R¹² is
hydrogen,
C₁-4 alkyl, unsubstituted or substituted with one or more of
hydroxy,
COOH,
amino,
25 aryl,
heteroaryl, or
heterocycloalkyl.

30 6. A compound of Claim 5, and pharmaceutically
acceptable salts thereof, wherein

A is

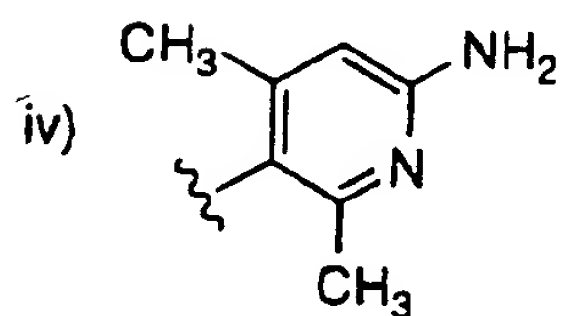
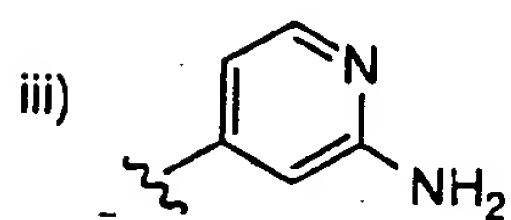
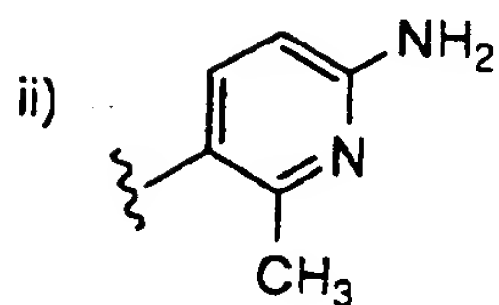
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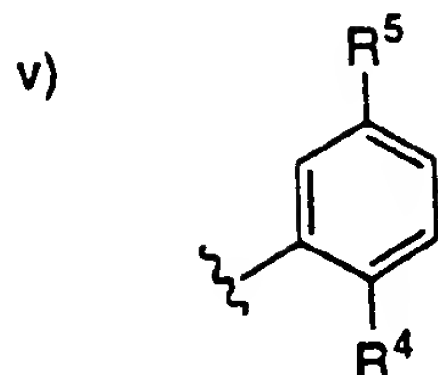
wherein

 R^5 is H, fluoro, chloro, and R^{10} and R^{11} are independently selected from

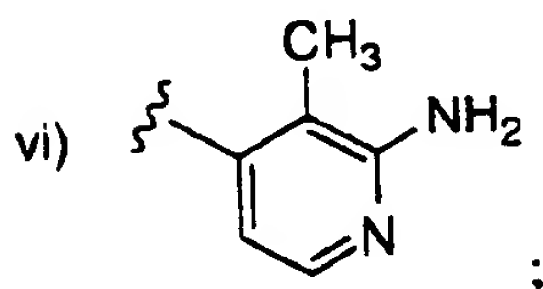
H,

 C_2H_5 , C_3H_5 , $(CH_2)_2N(CH_3)_2$, C_3 cycloalkyl,

- 152 -



wherein R⁴ is OH, chloro, H, -OCH₂CN, fluoro, -OCH₂COOH,
and R⁵ is chloro or CF₃,



5

R³ is CH₃, or CH₂CH₃;

X is H or chloro; and

10

W is

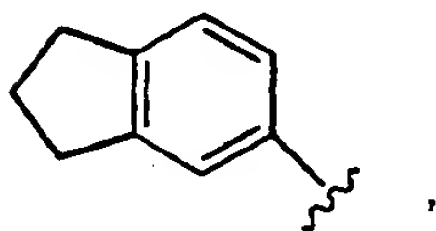
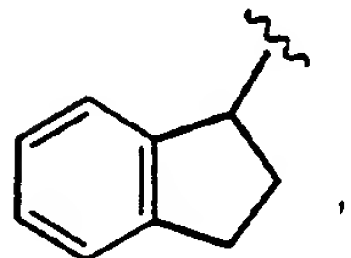
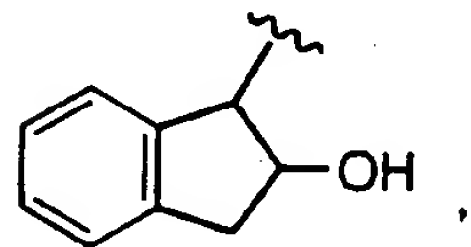
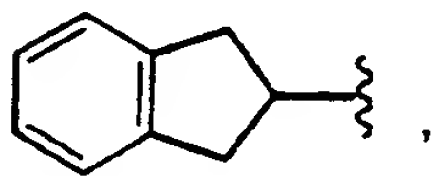
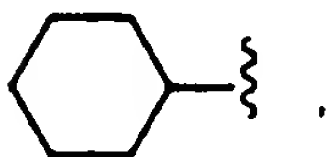
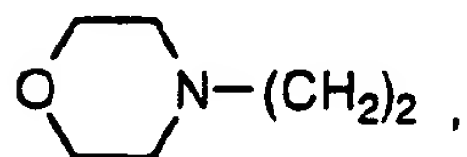
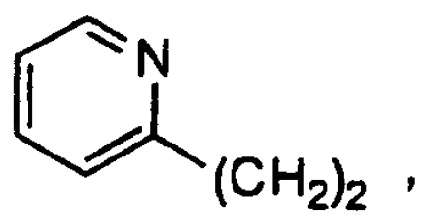
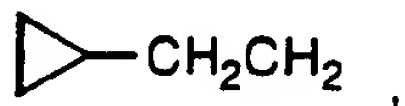
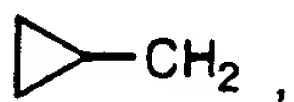
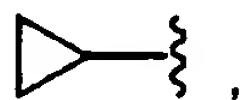
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PhCH₂CH₂,
(CH₃)₃C-,
HOOCCH₂,
CF₃CH₂,
(CH₃)₂N(CH₂)₂,
PhCH₂O(CH₂)₂,
PhCH(CH₃),
20 PhCH₂CH(COOH),
CH₃(CH₂)₅,
PhCH₂,
H,
CH₃(CH₂)₄,
25 CH₃CH₂CH(CH₃)CH₂,
(Ph)₂CHCH₂,

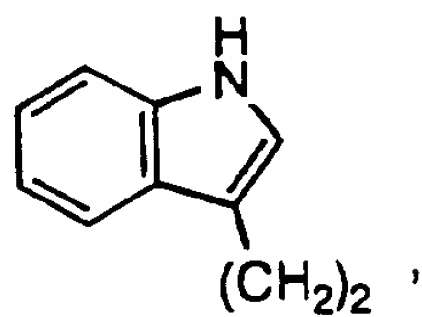
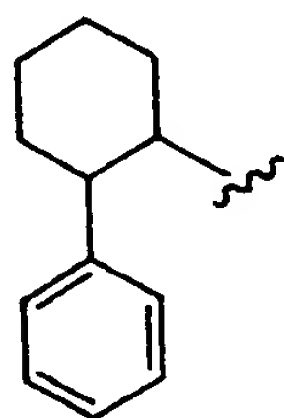
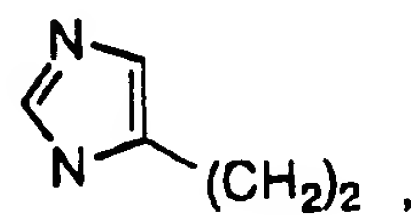
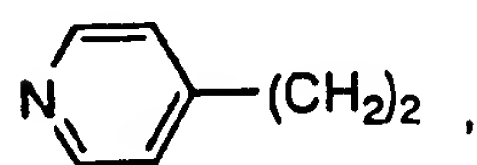
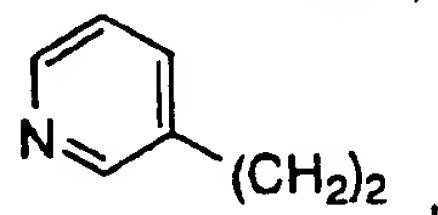
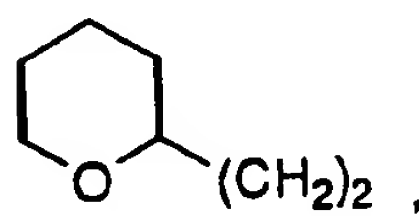
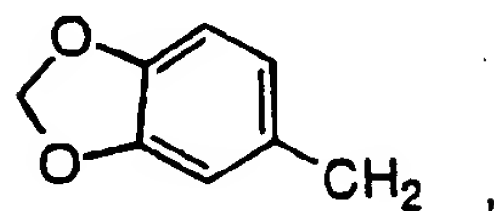
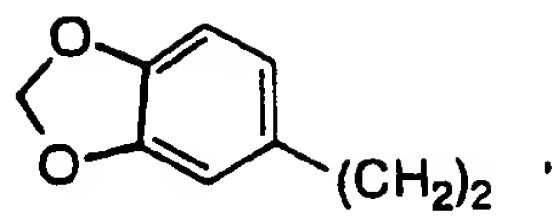
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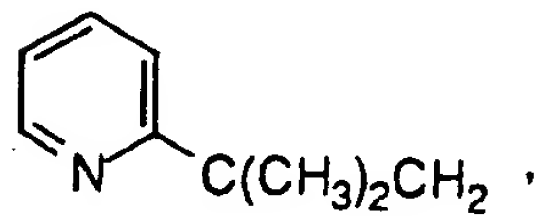
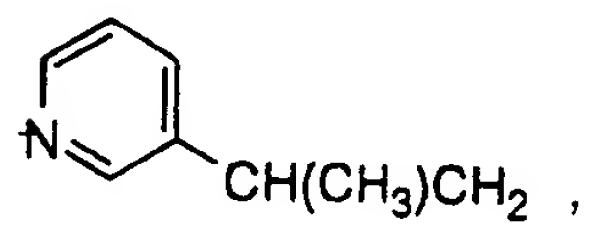
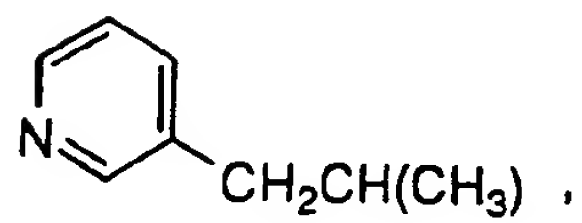
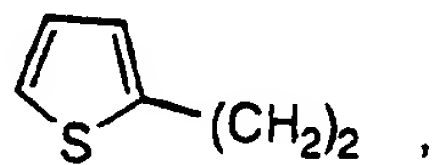
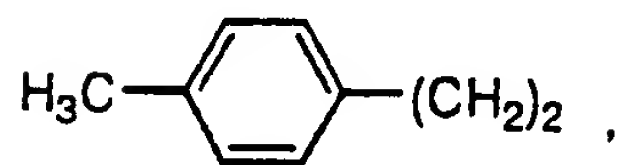
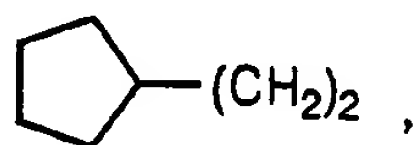
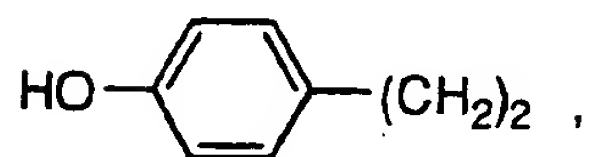
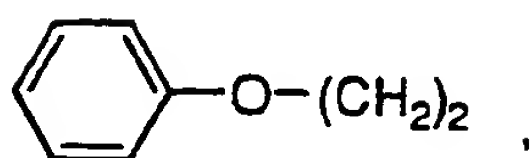
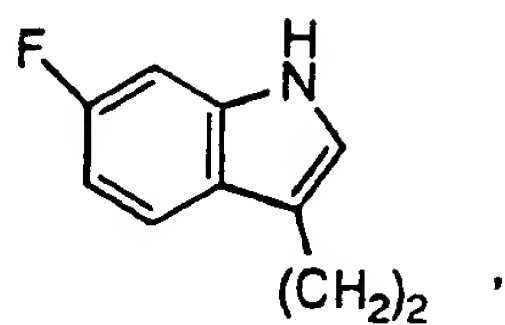
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PhCH₂C(CH₃)₂,
PhCH(CH₃)CH₂,
(CH₃)₂CH,
PhCH(OH)CH₂,
PhC(CH₃)CH₂,
(Ph)₂CHCH₂,



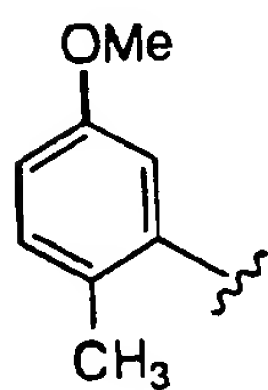
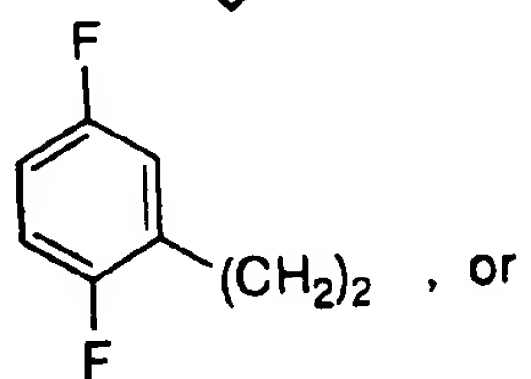
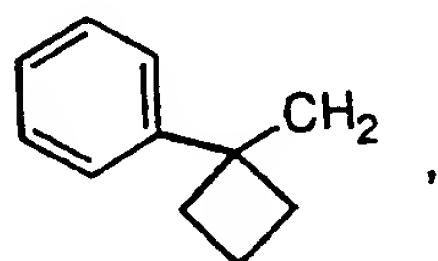
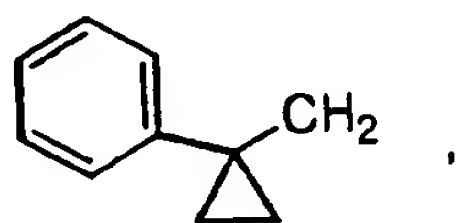
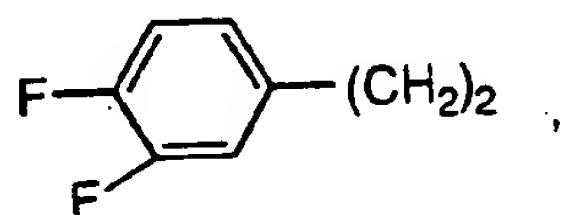
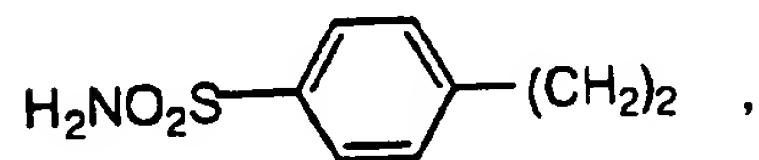
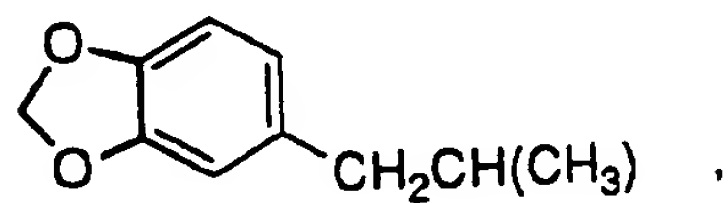
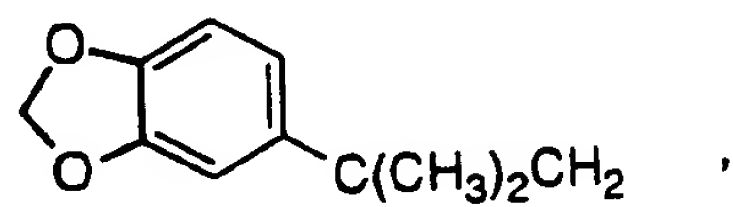
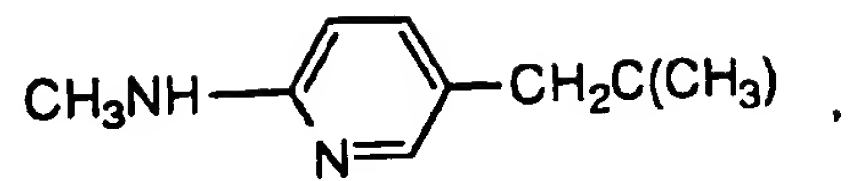
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- 155 -

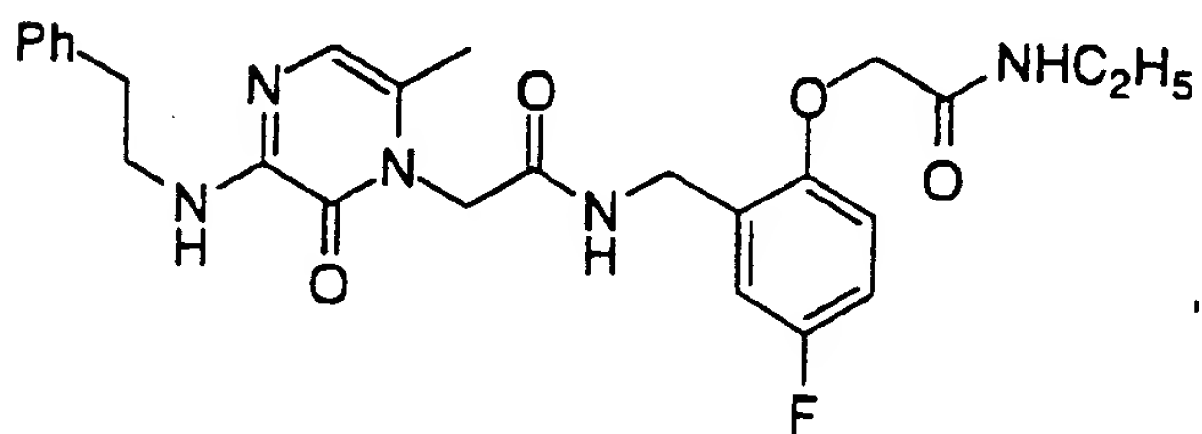
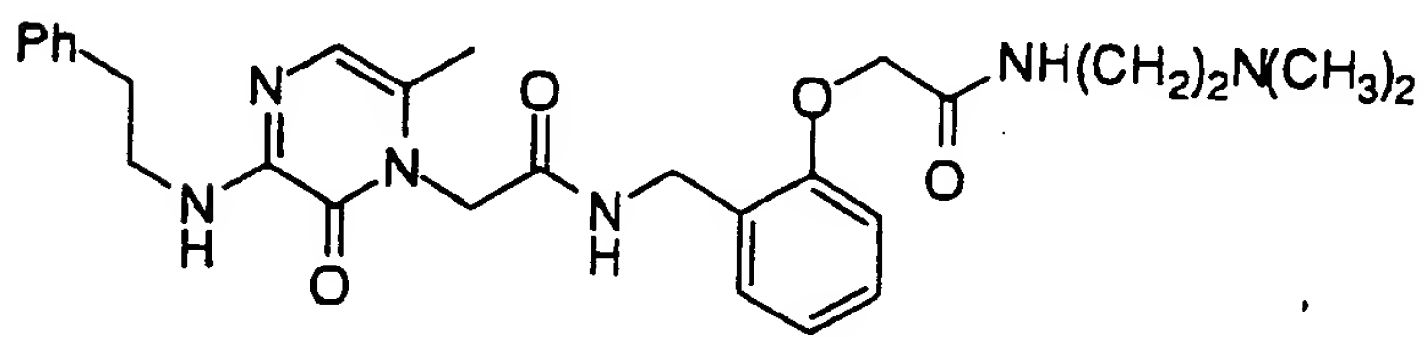
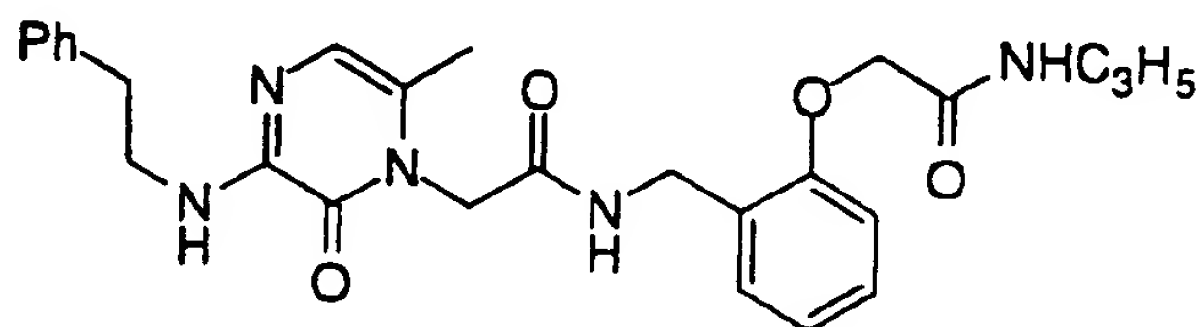
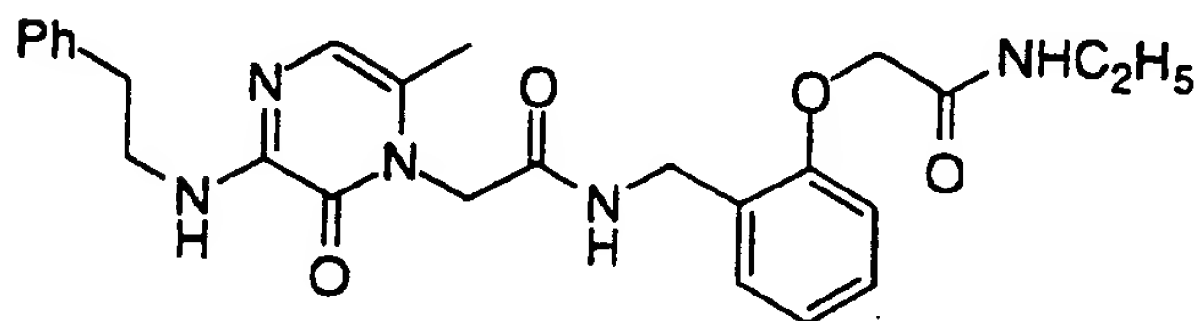


- 156 -

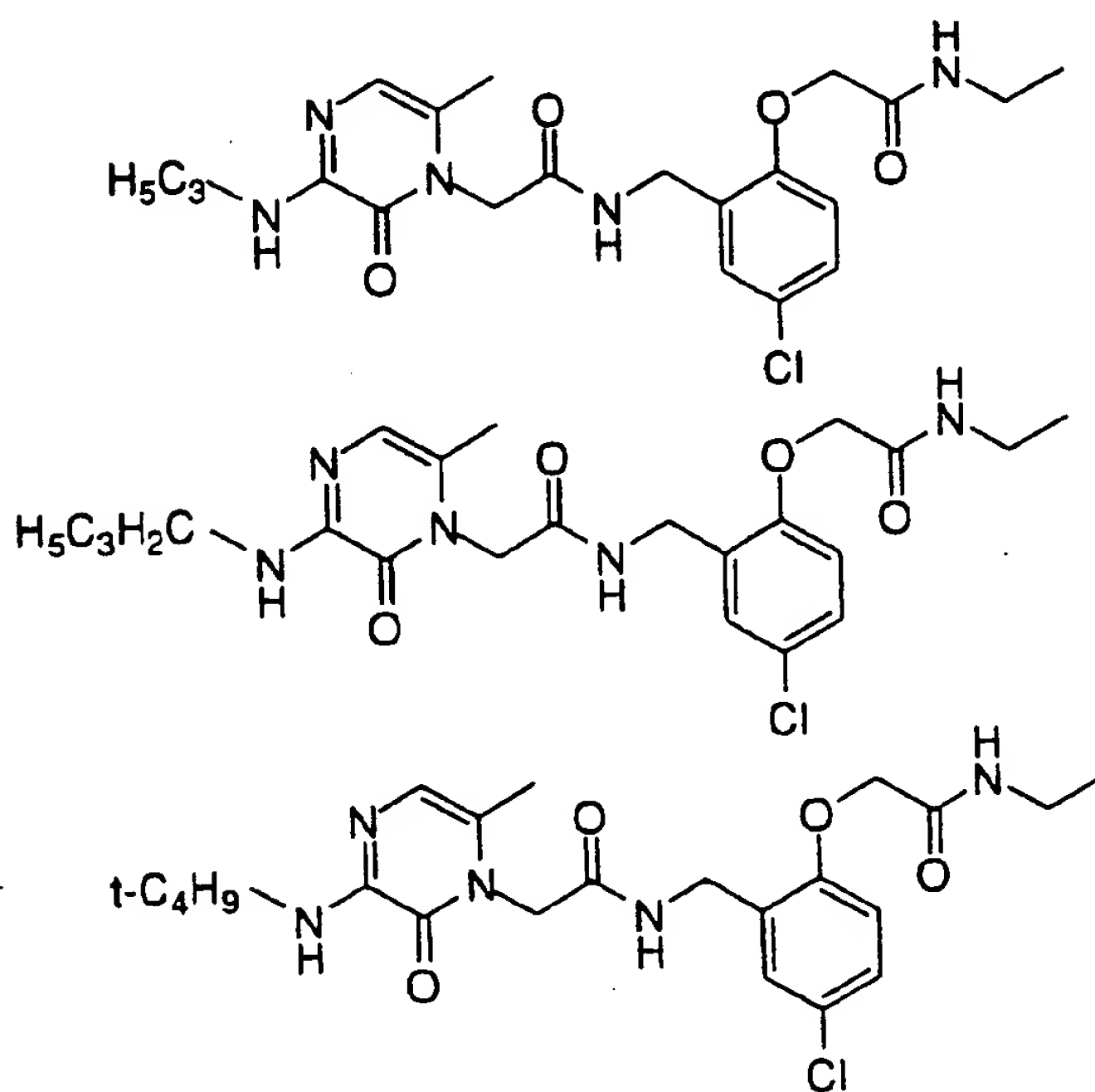
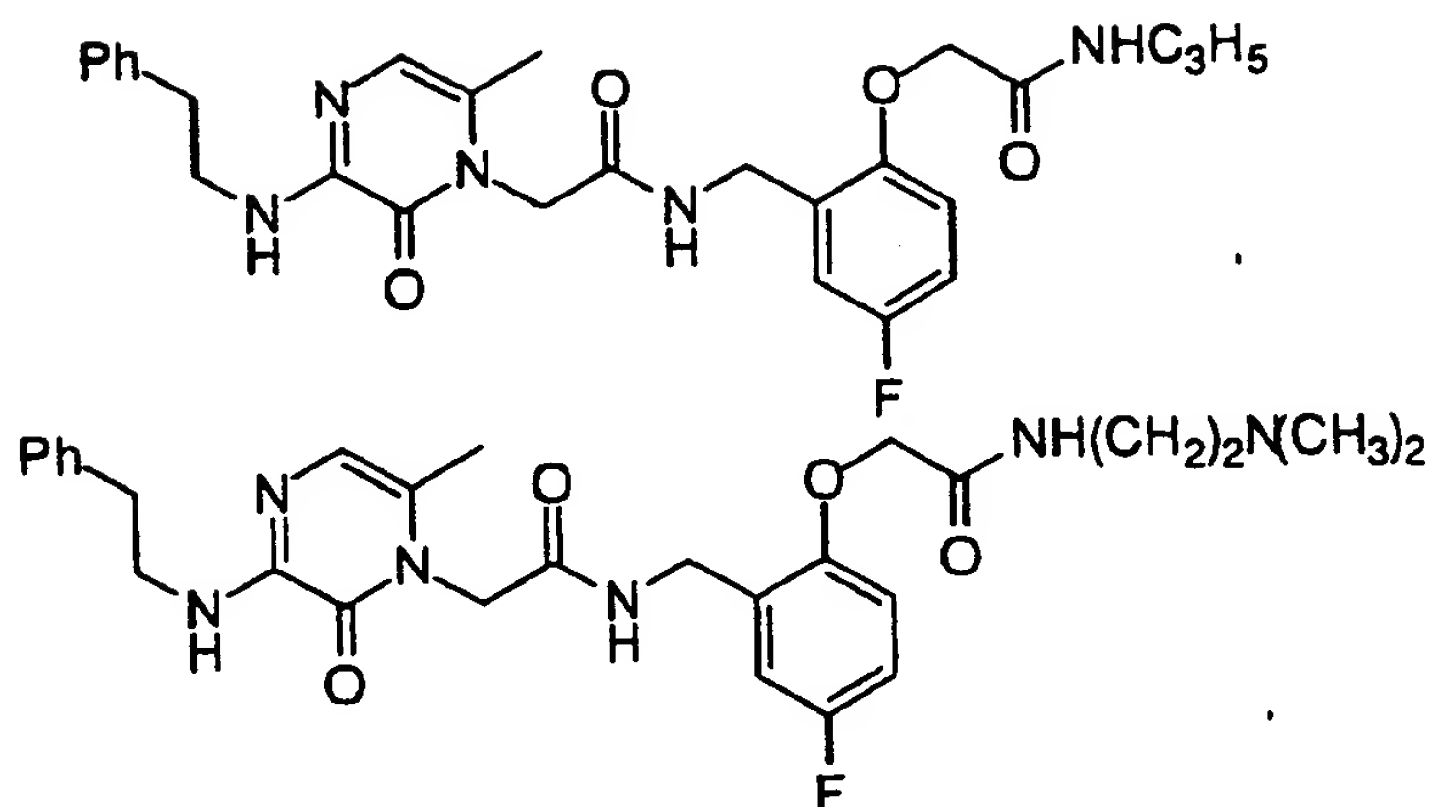


- 157 -

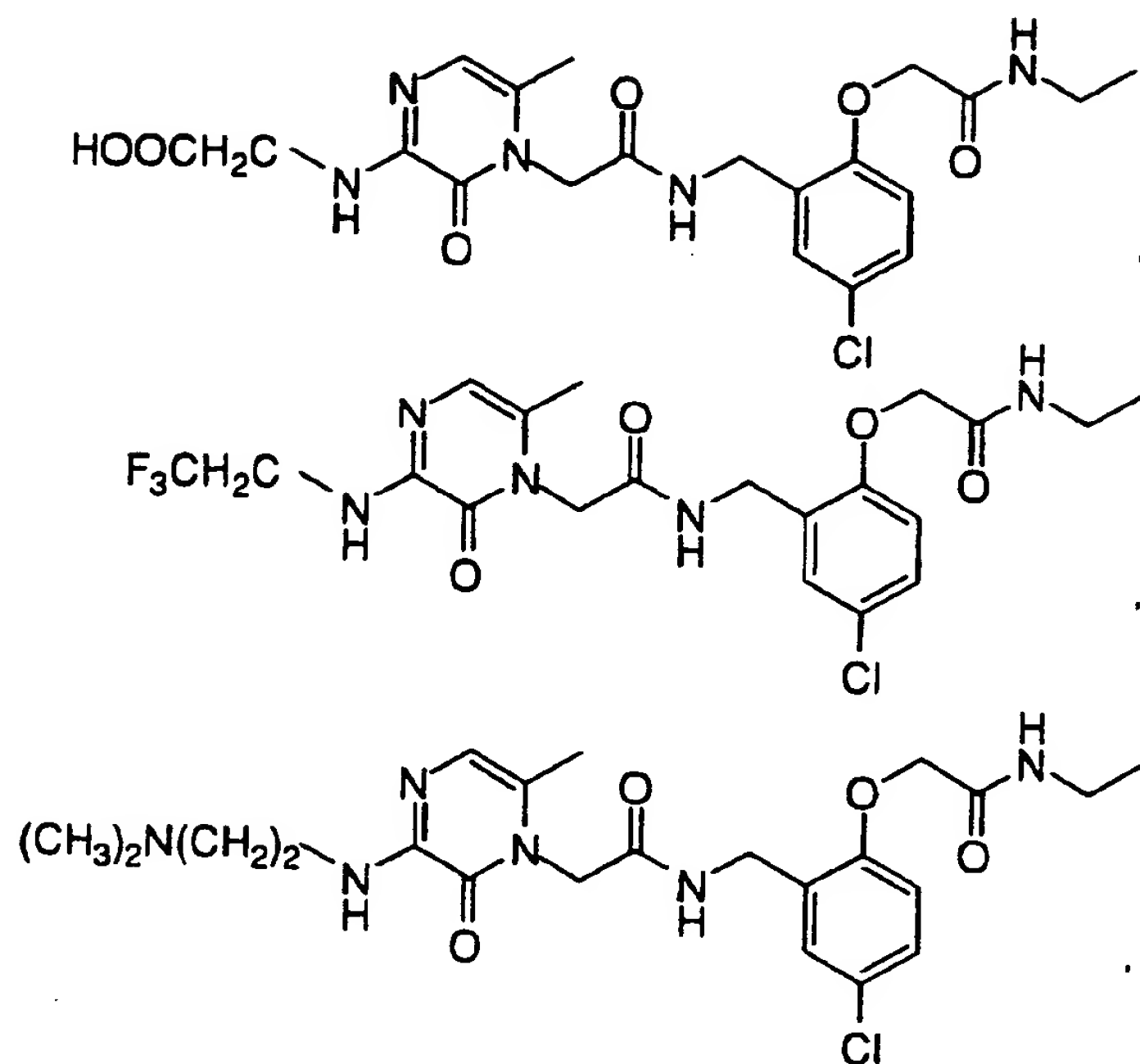
7. The compound of Claim 6, and pharmaceutically acceptable salts thereof, selected from the group consisting of:



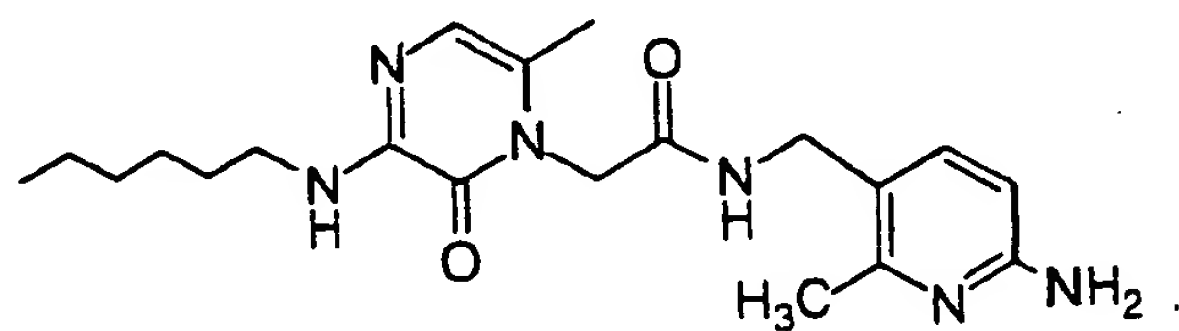
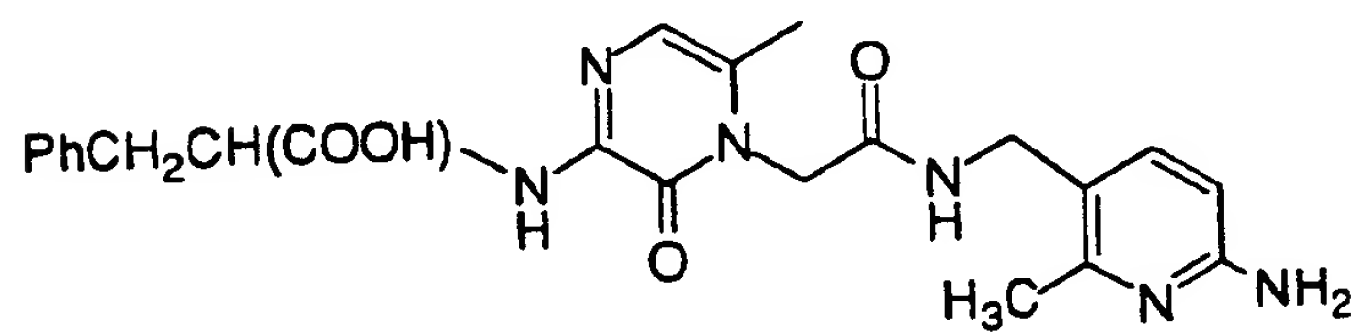
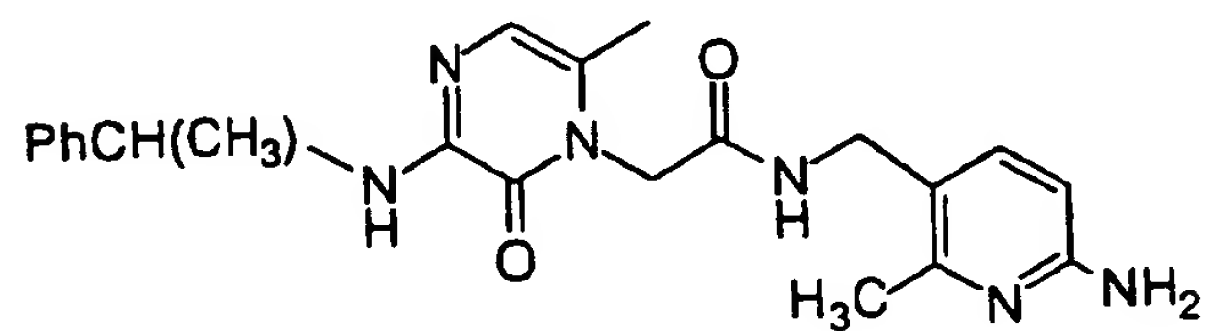
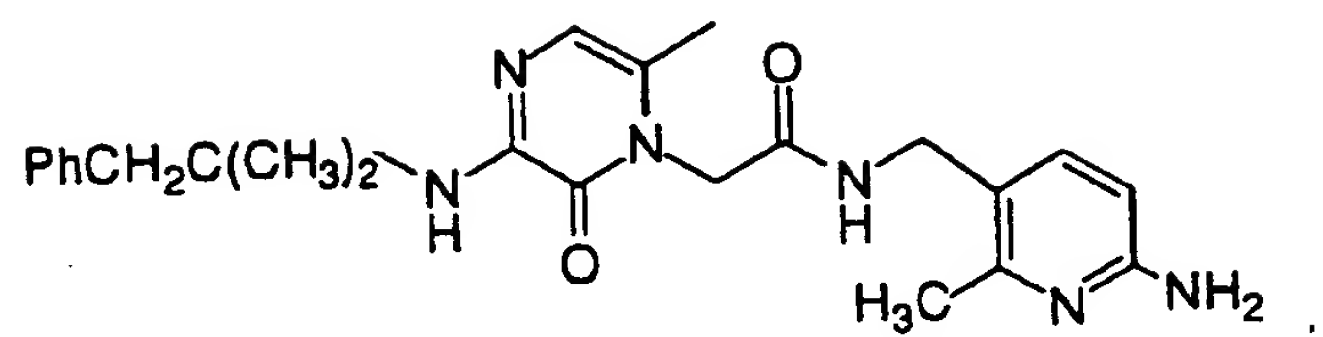
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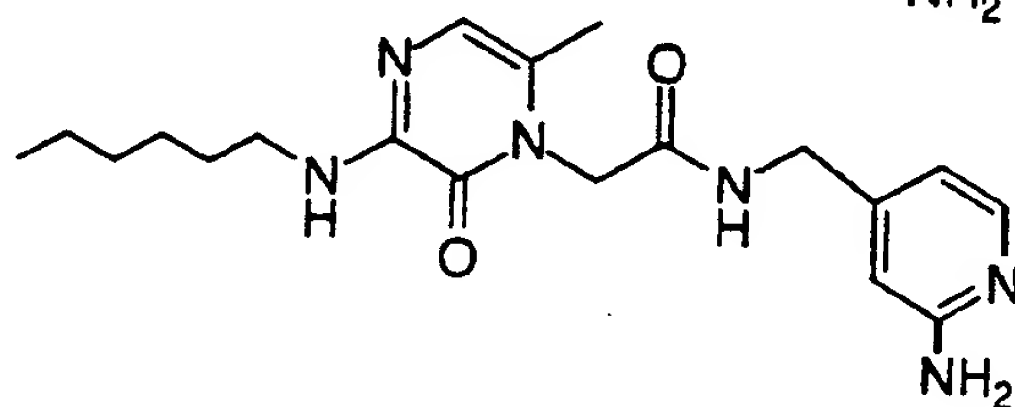
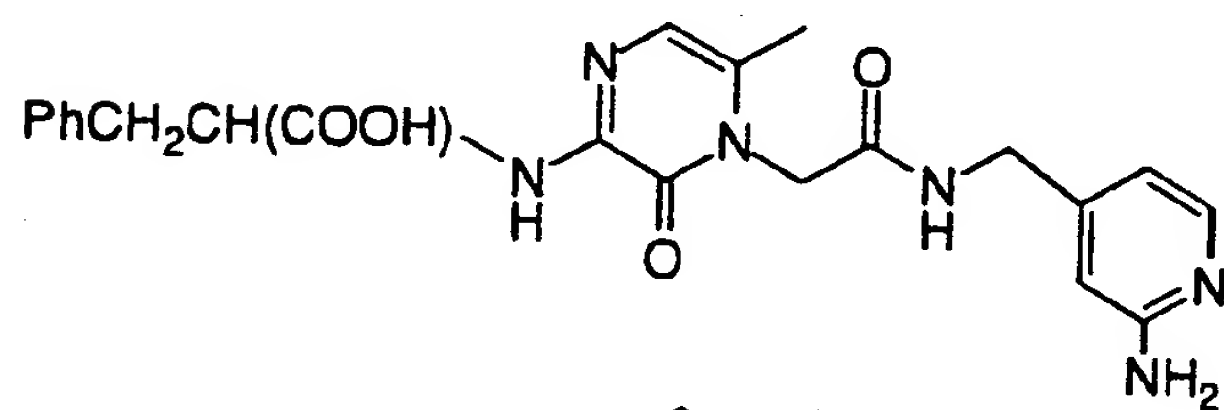
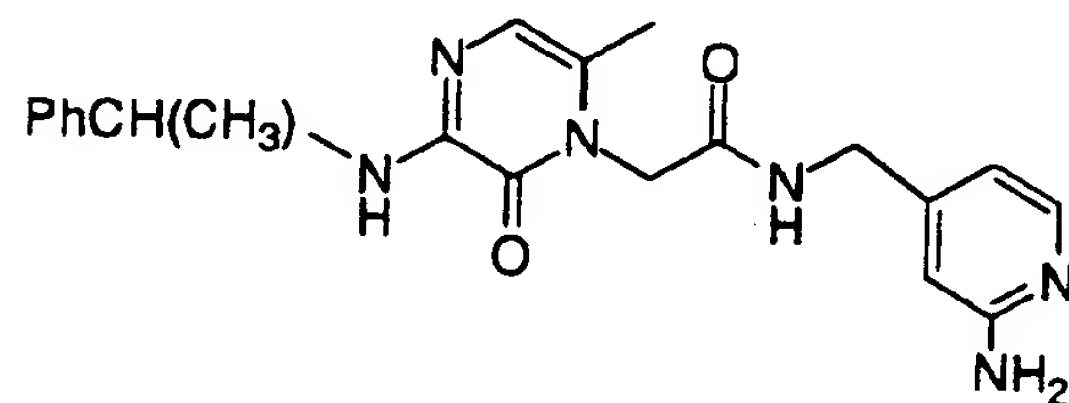
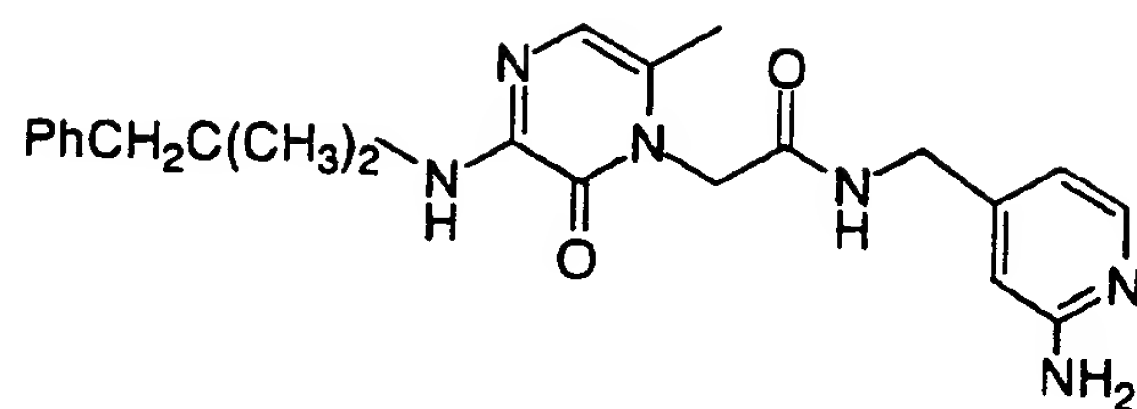
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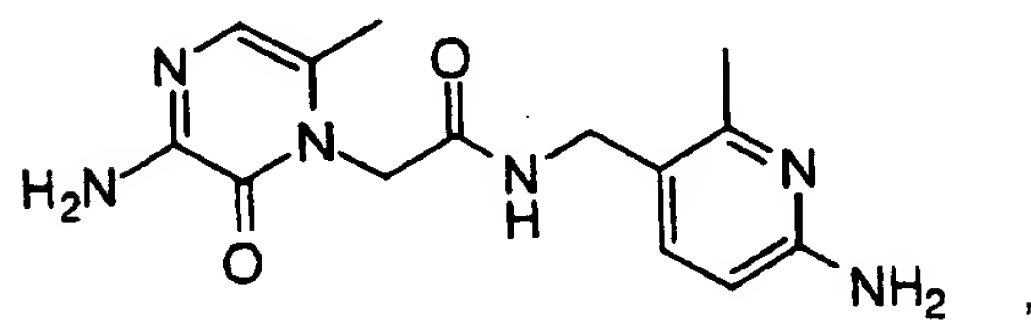
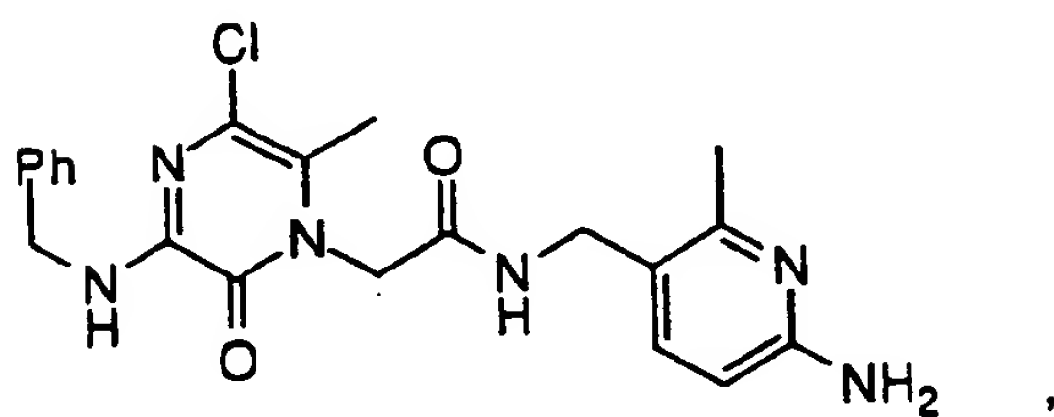
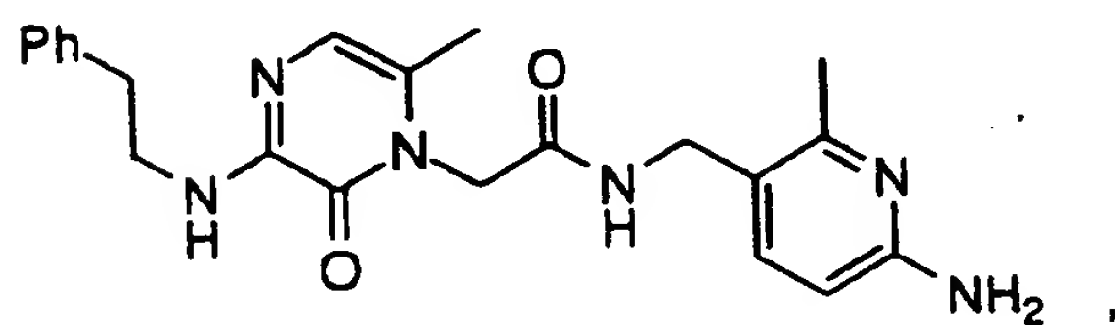
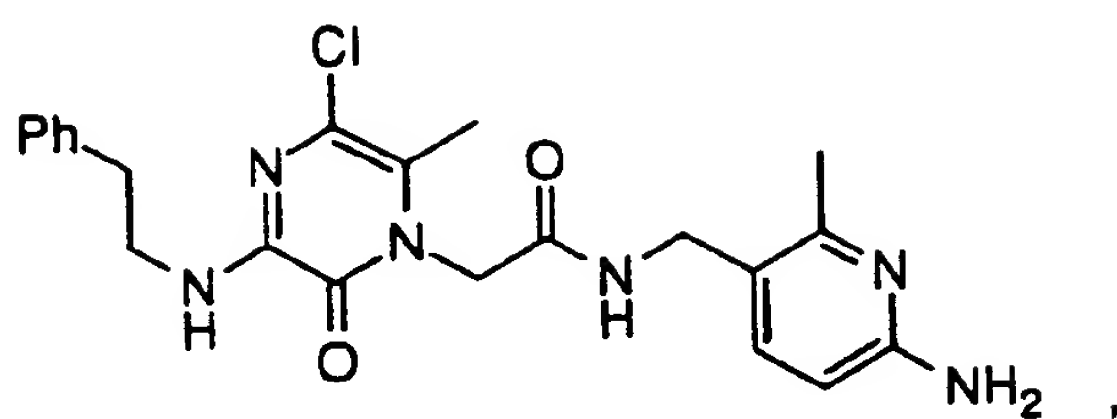
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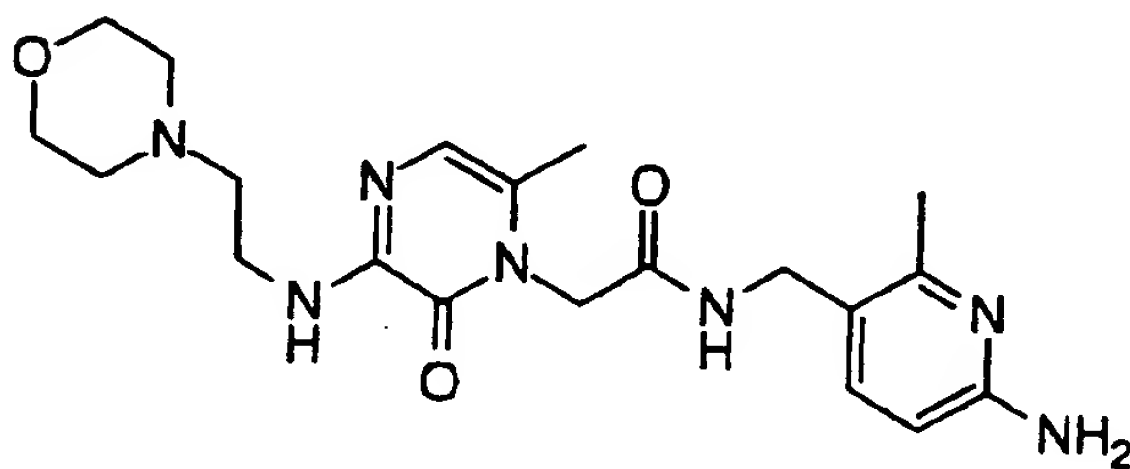
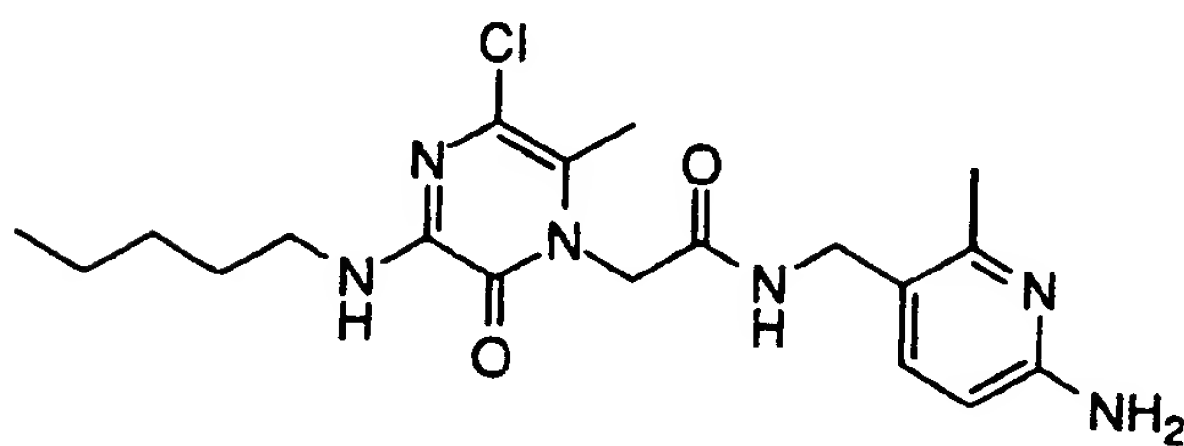
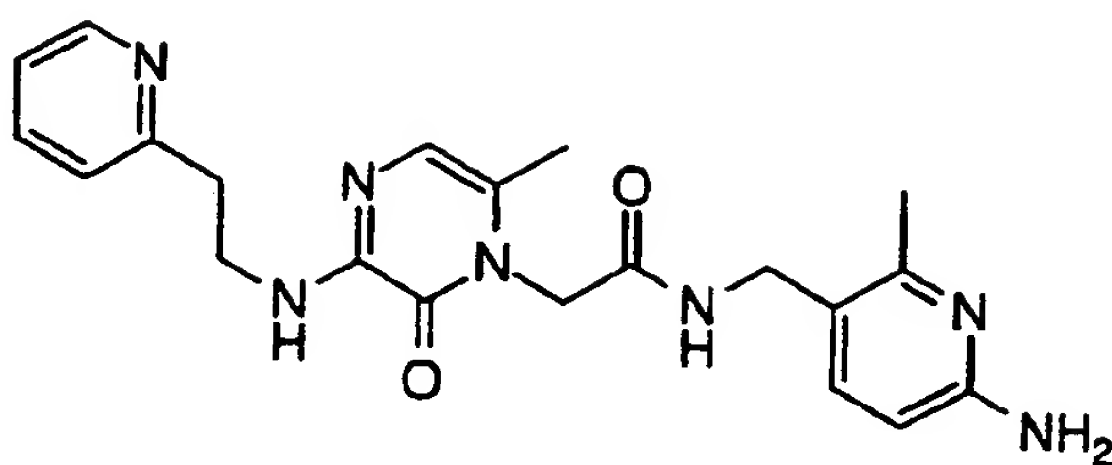
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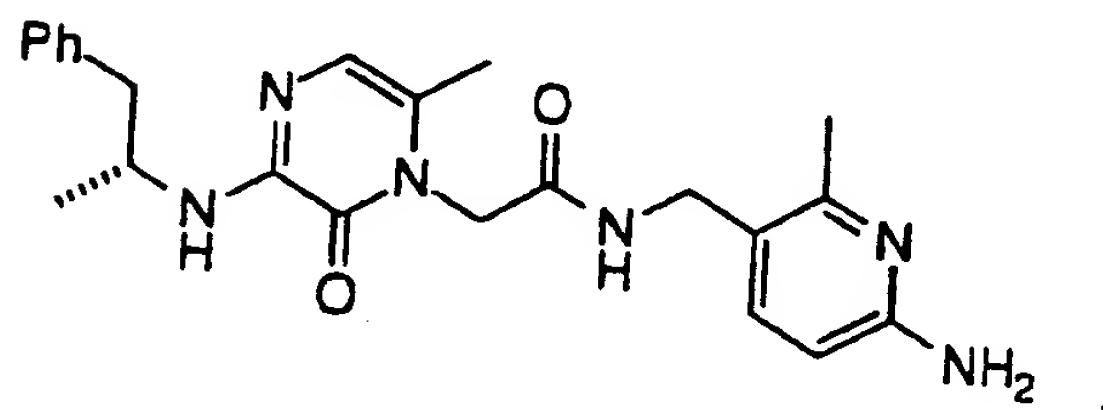
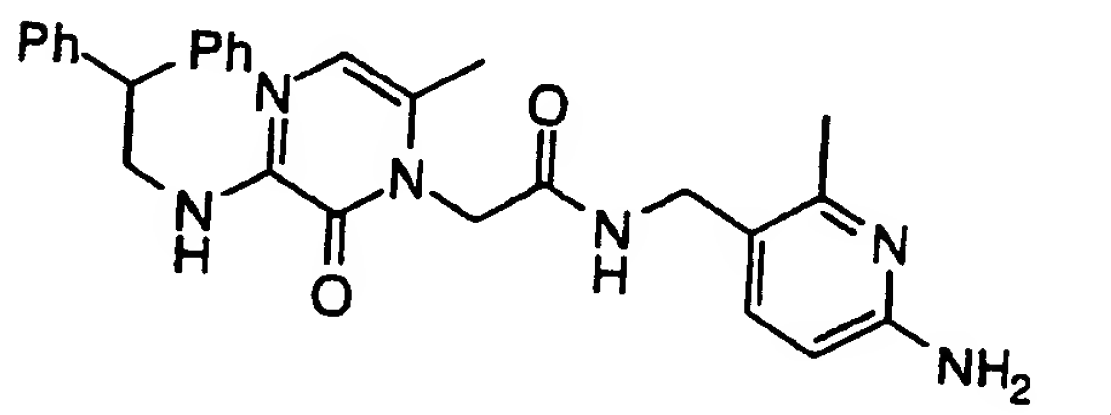
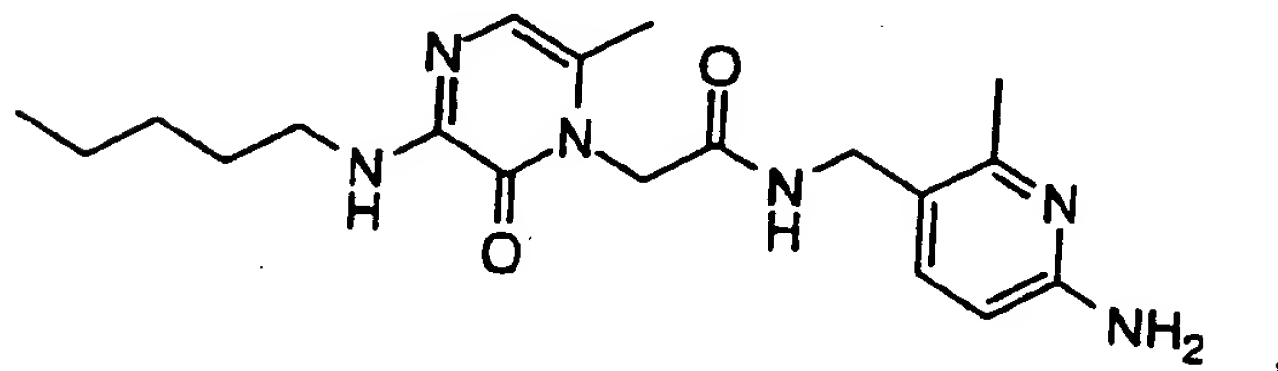
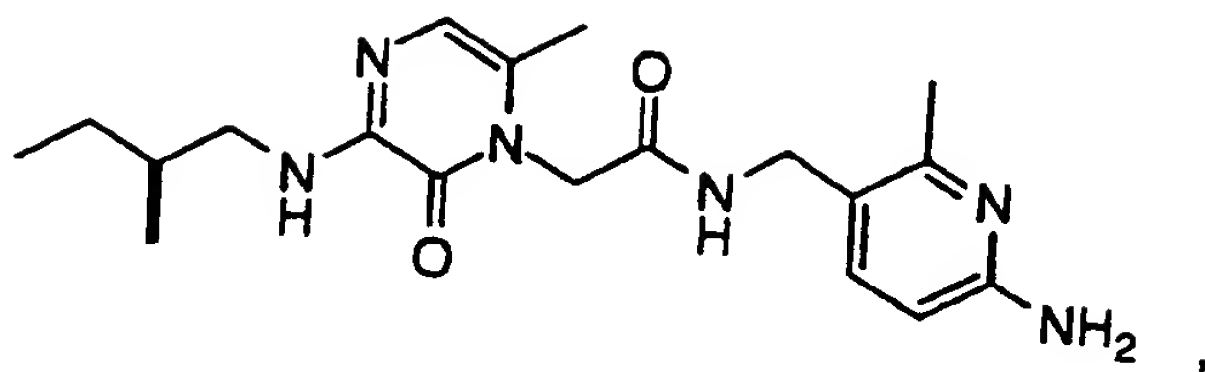
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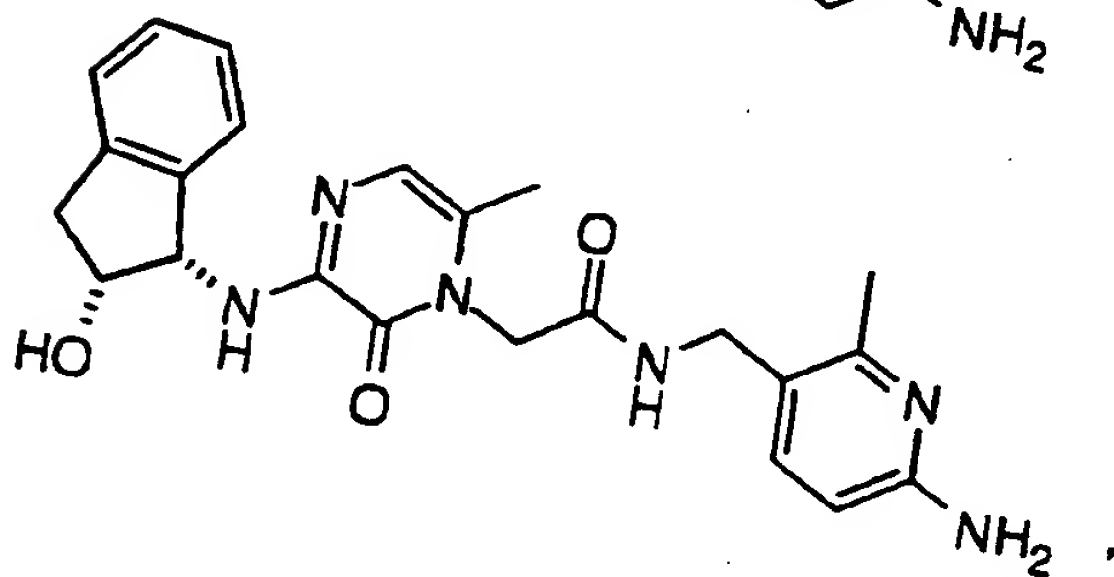
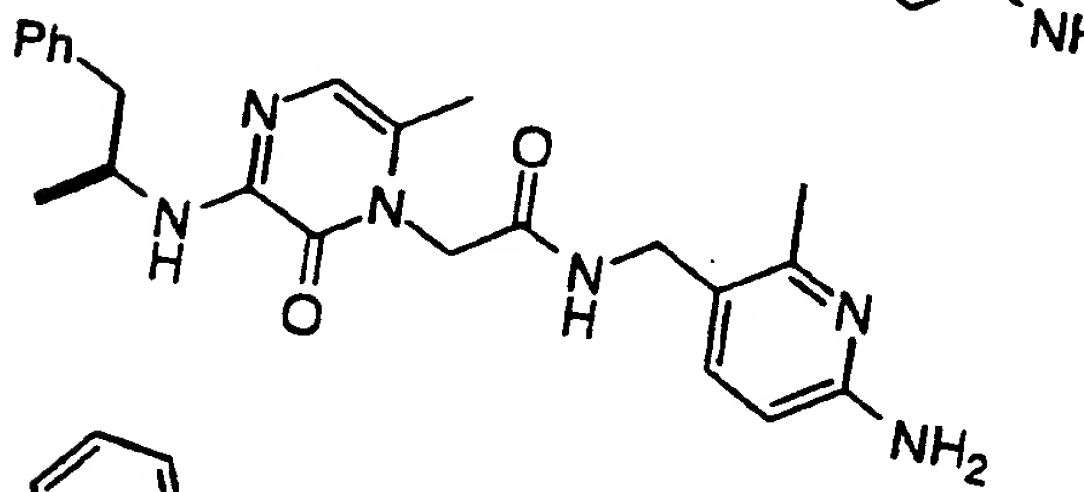
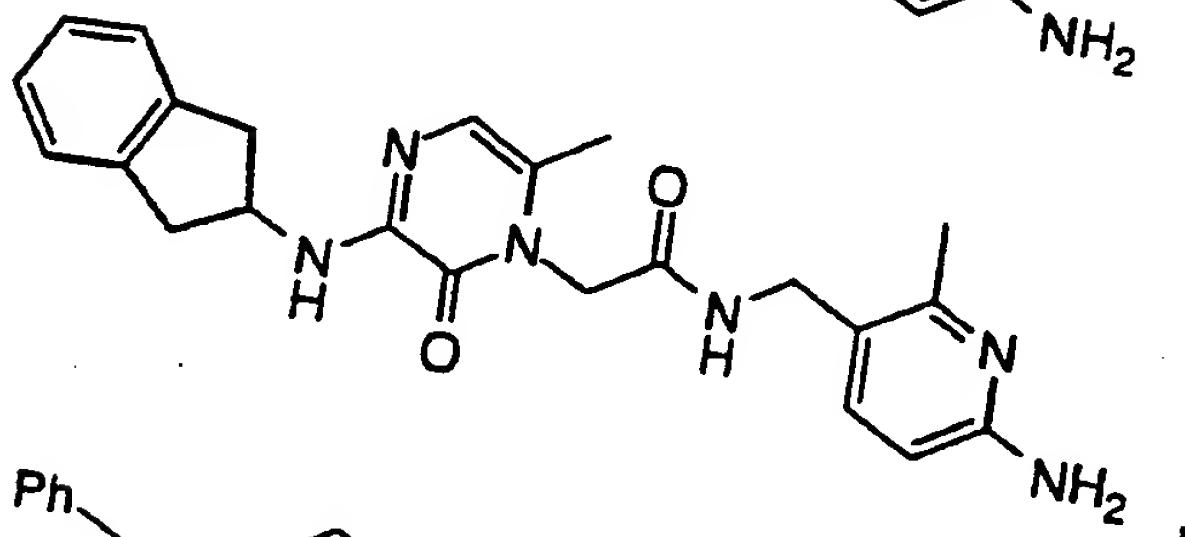
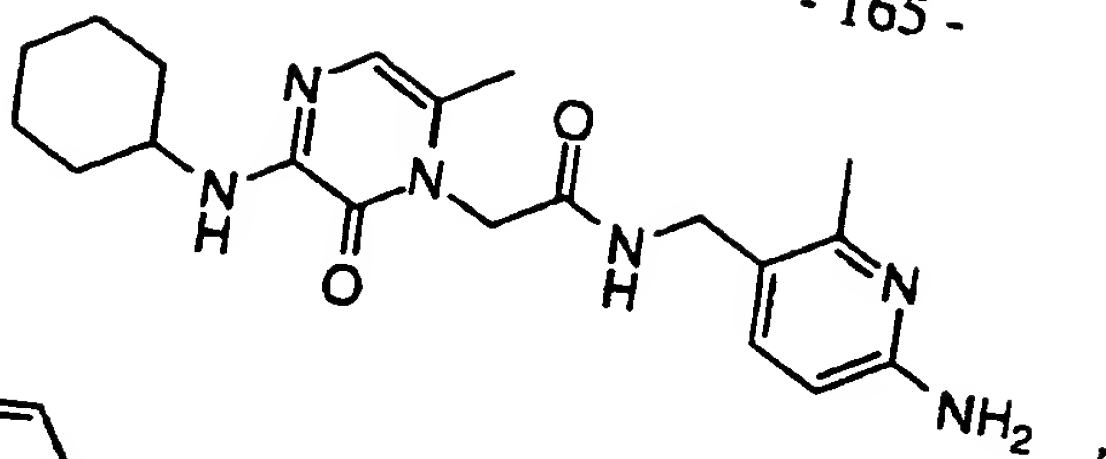
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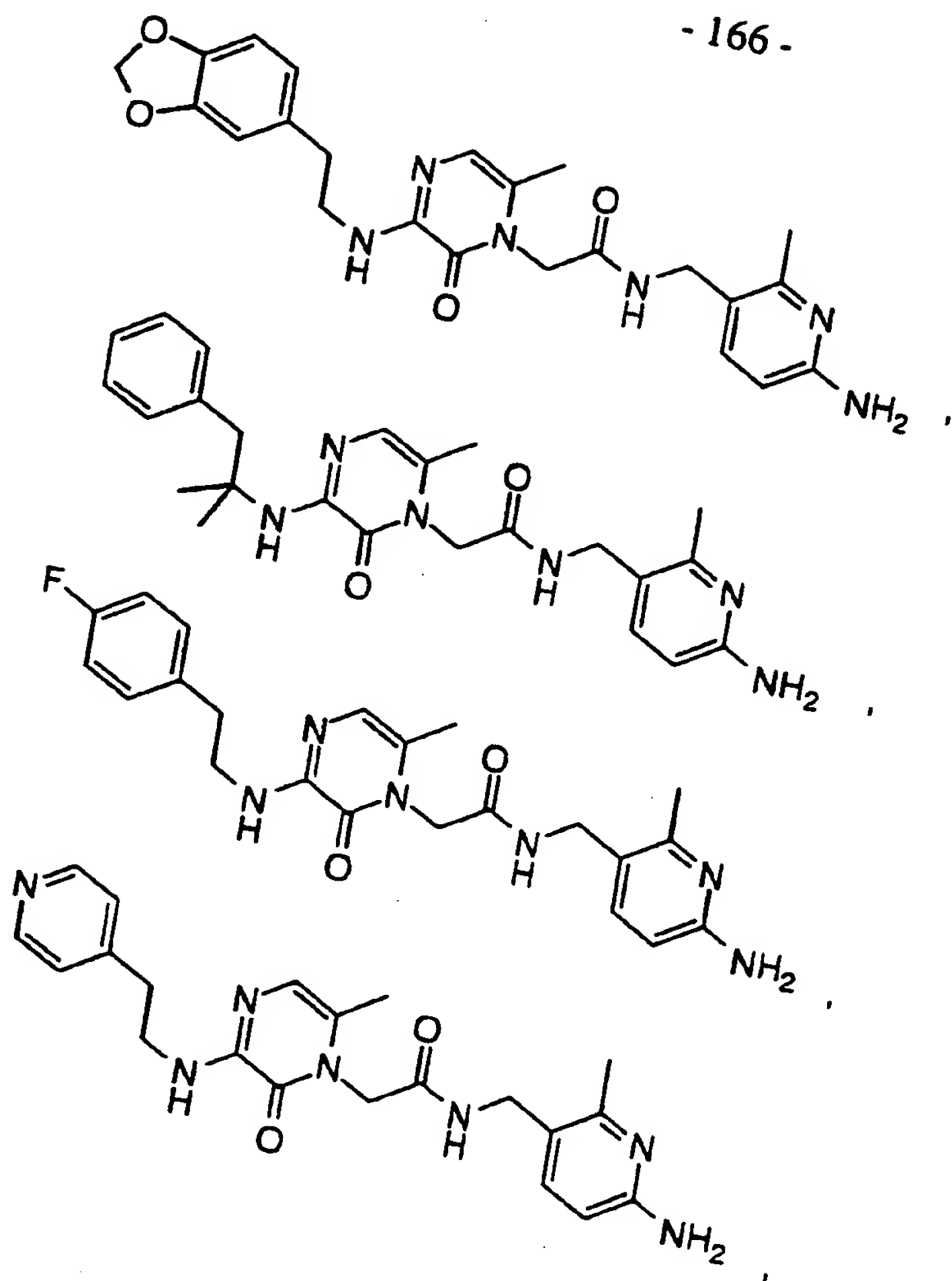
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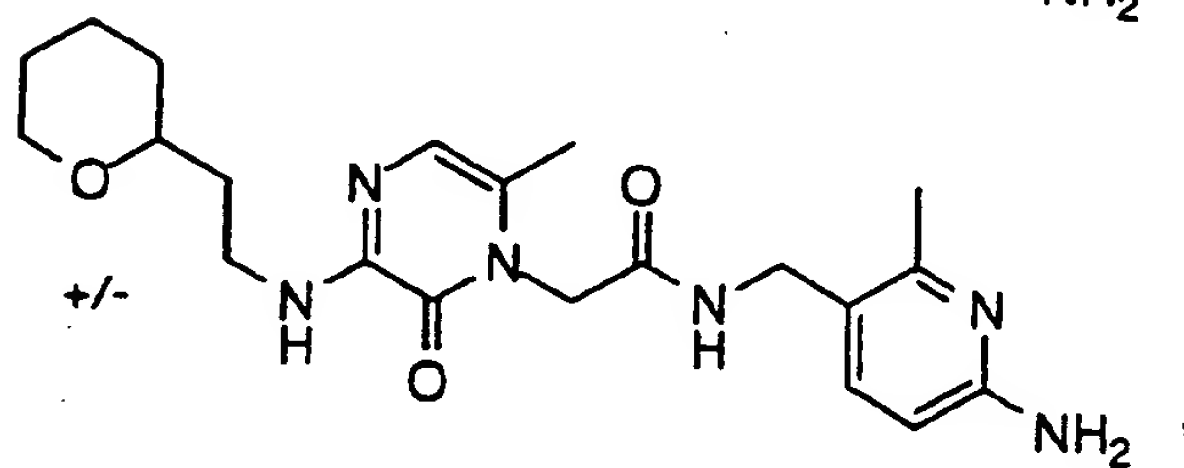
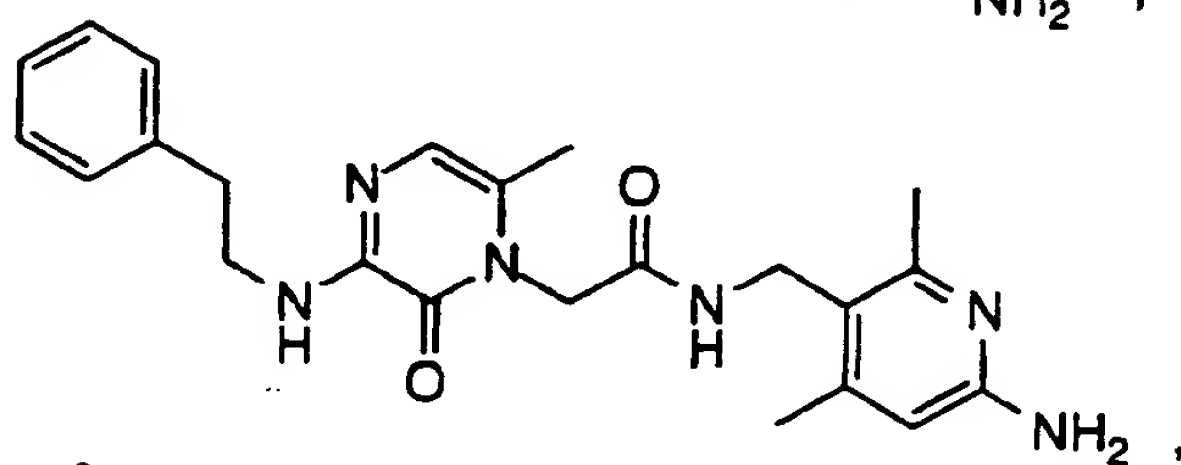
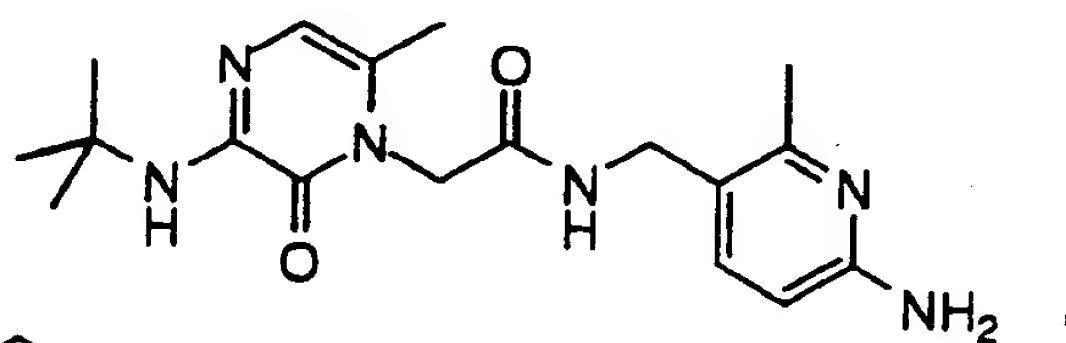
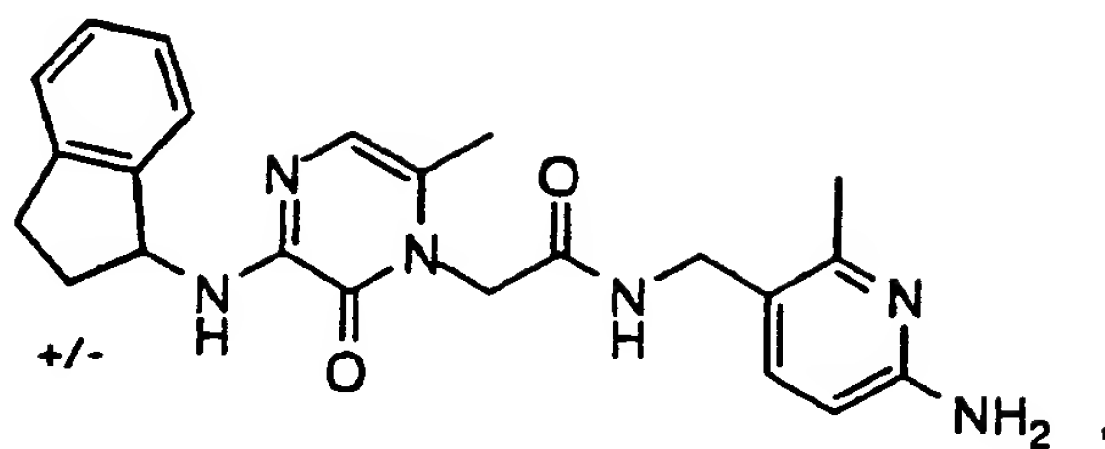
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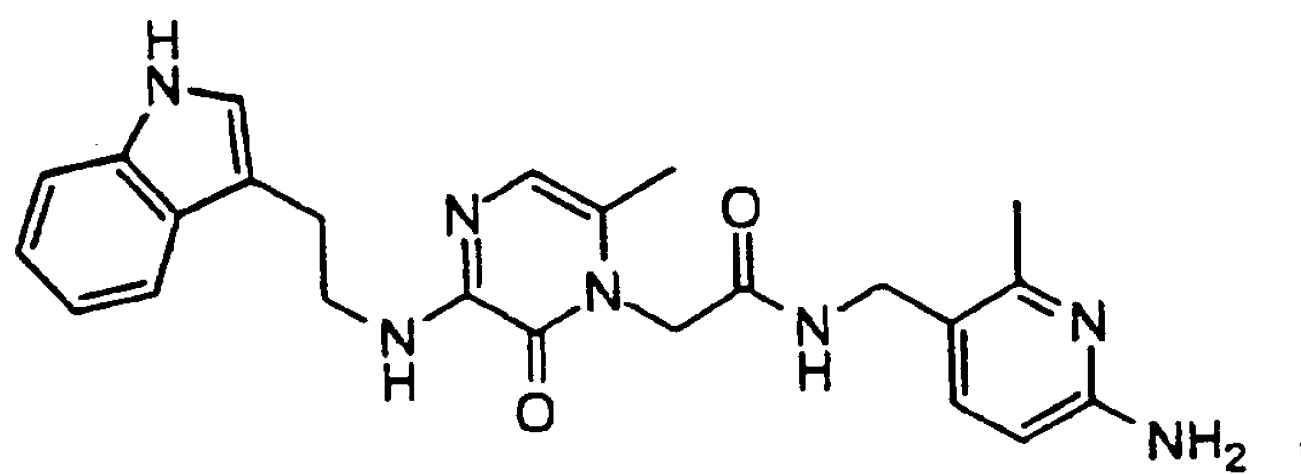
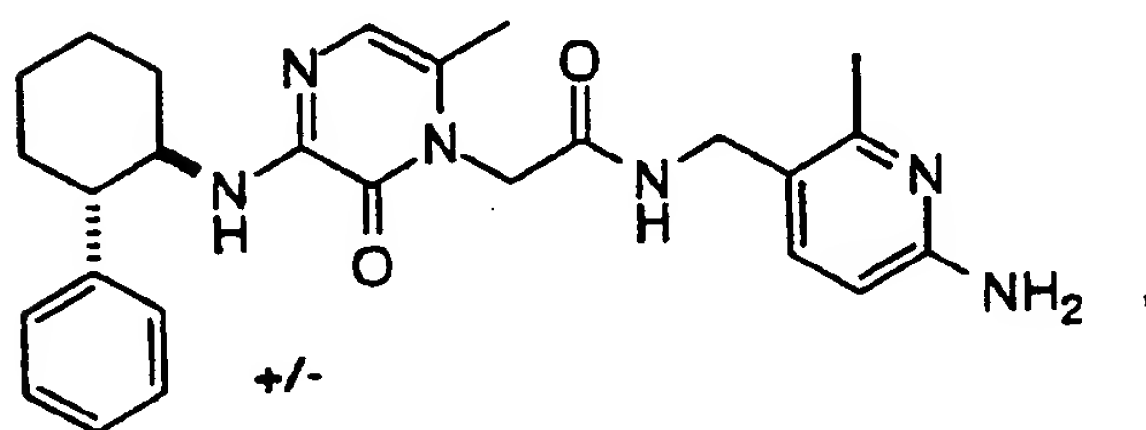
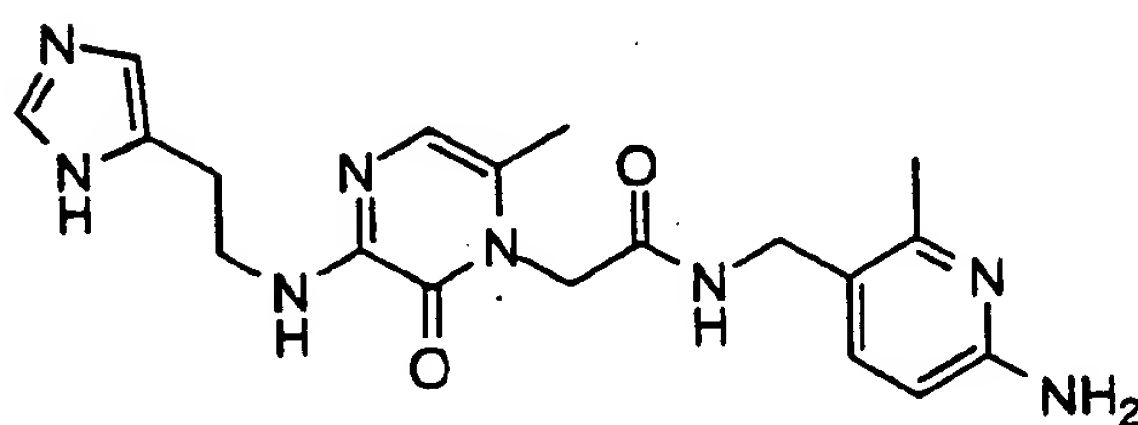
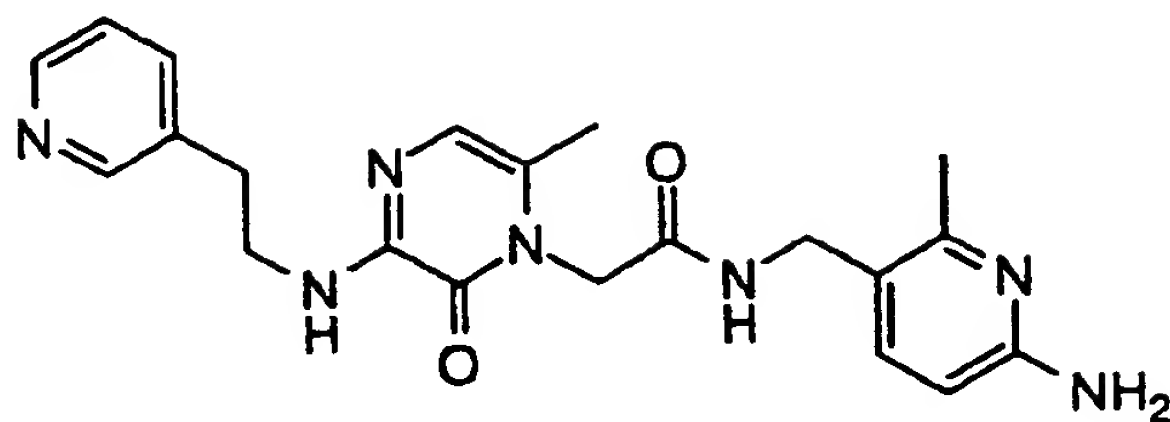
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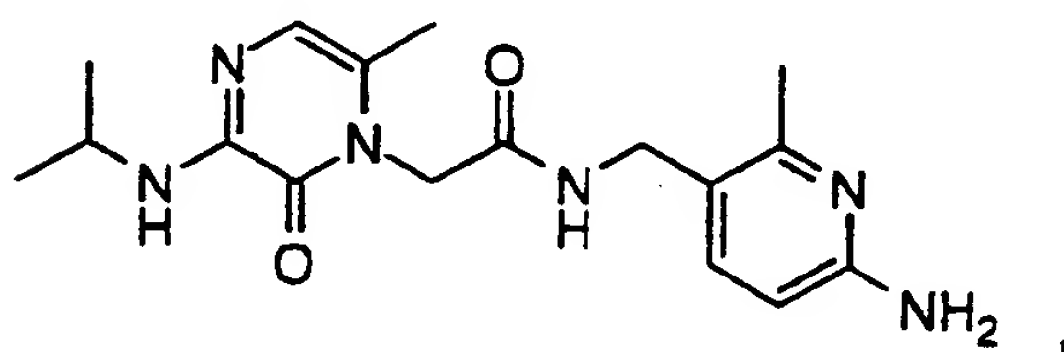
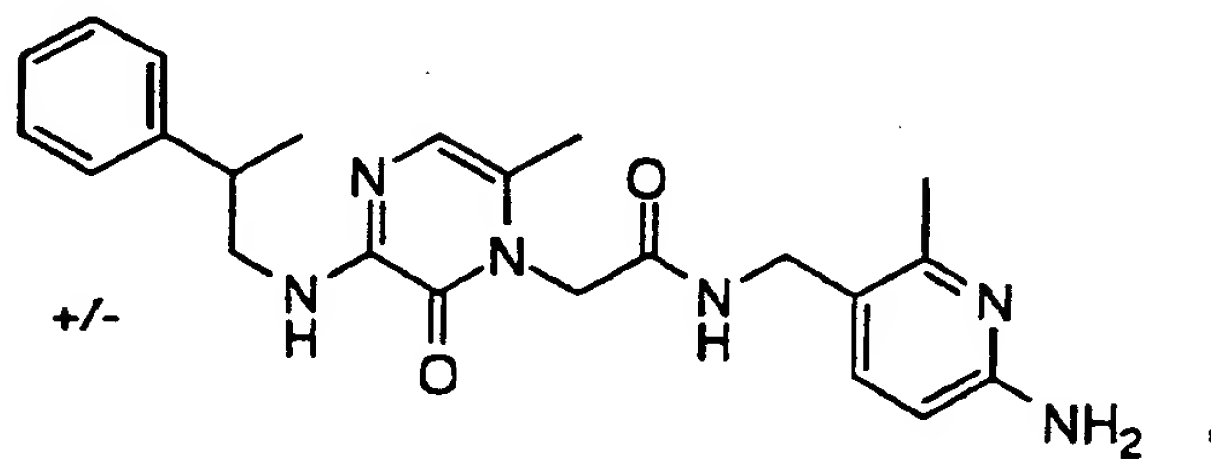
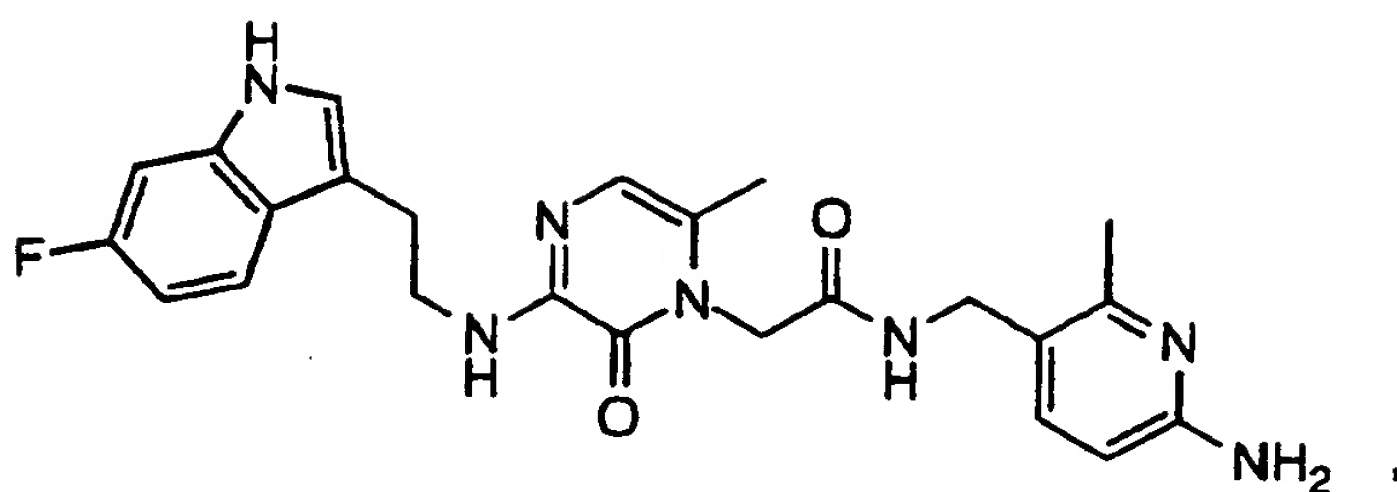
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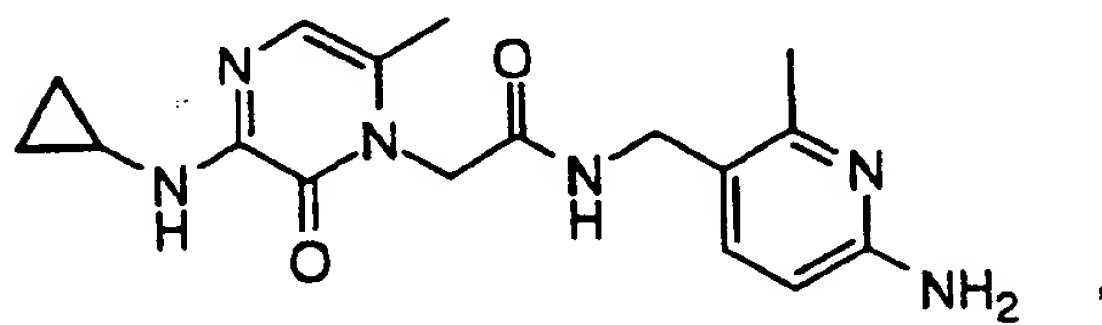
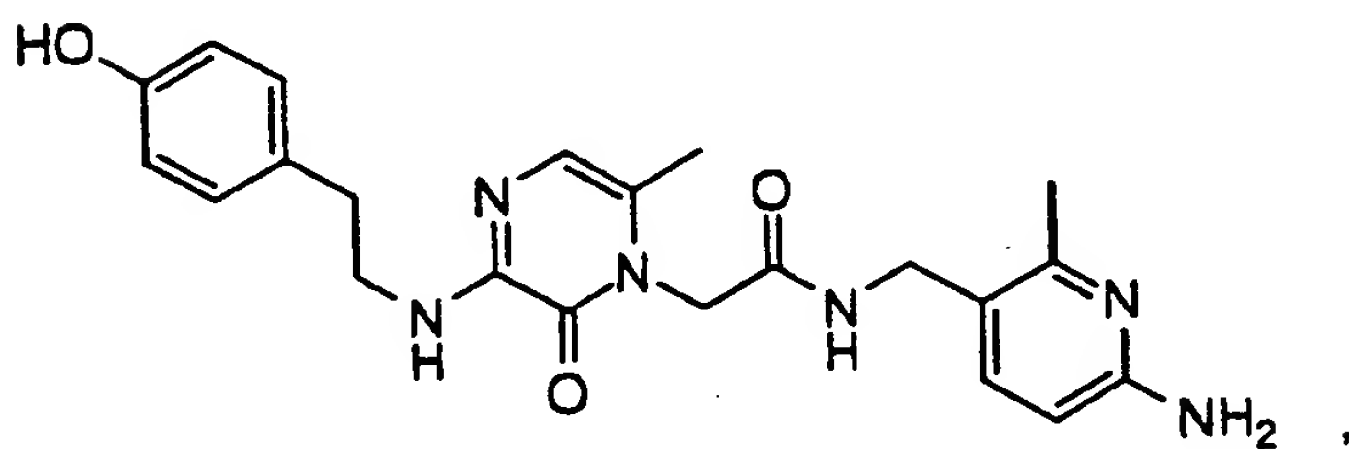
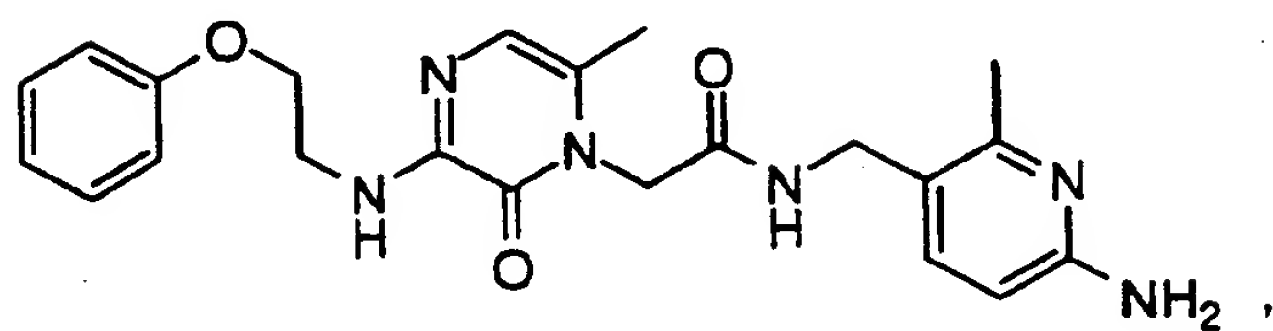
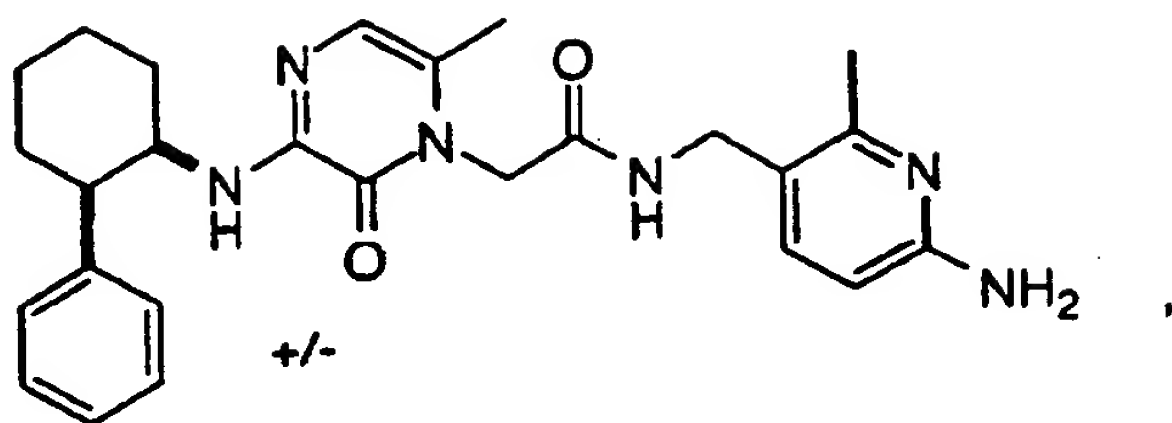
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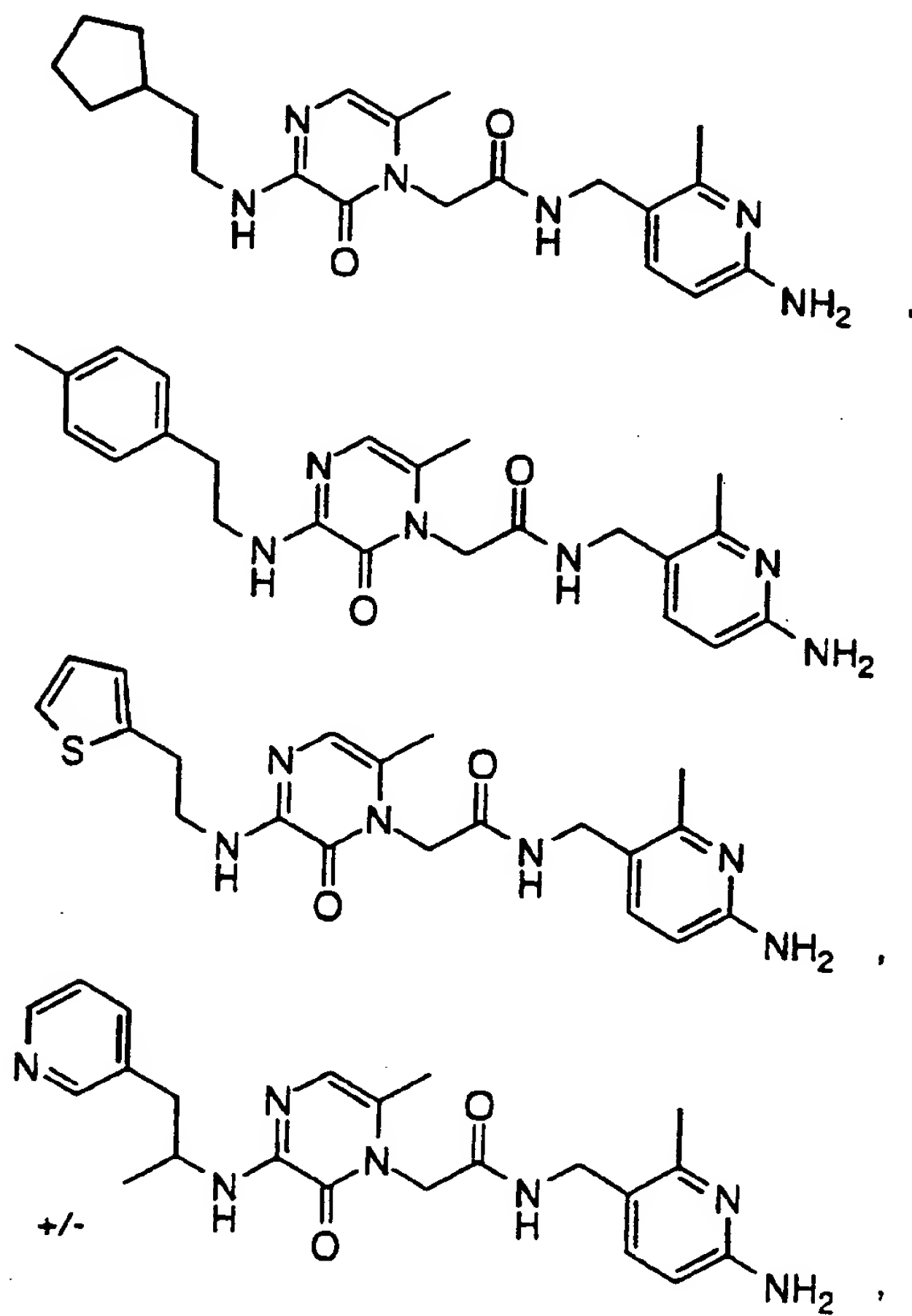
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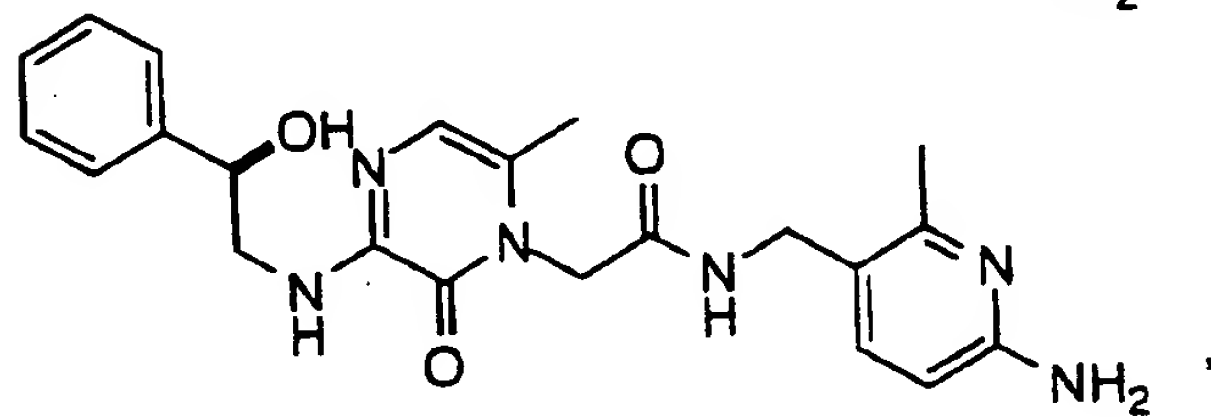
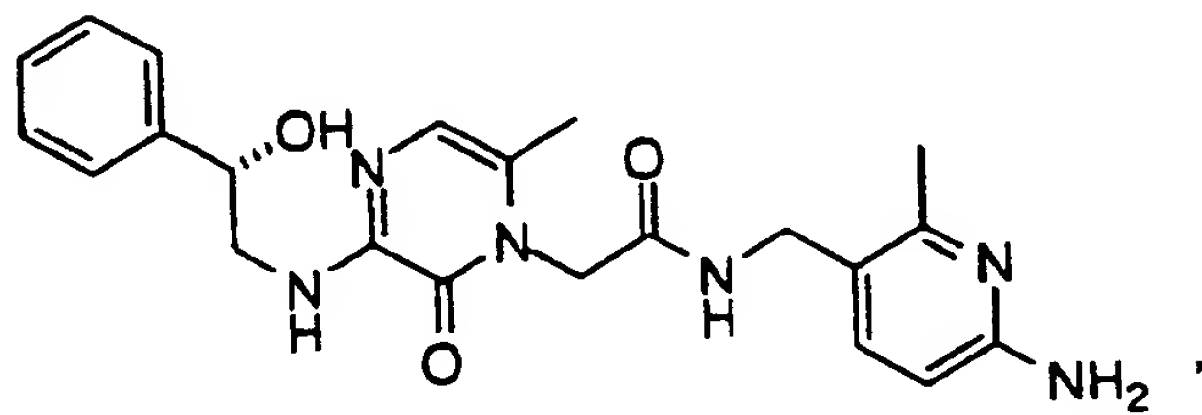
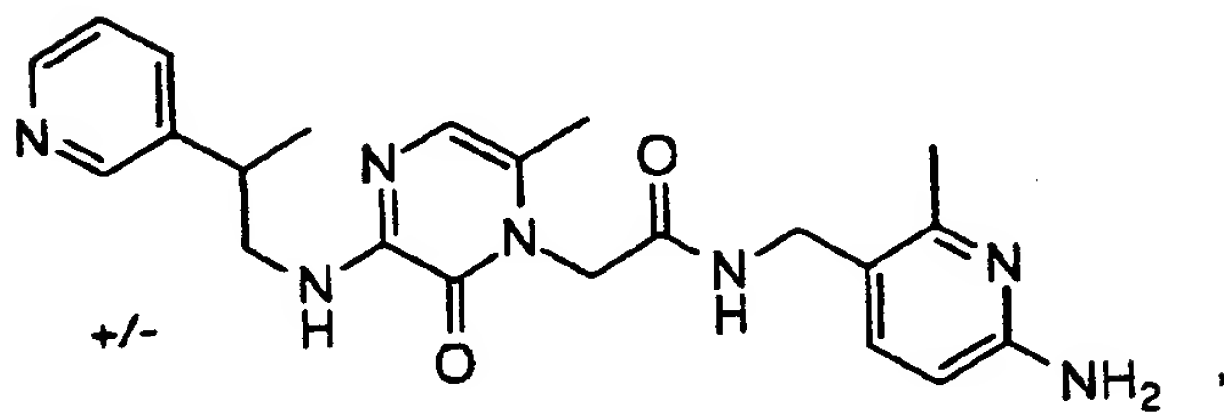
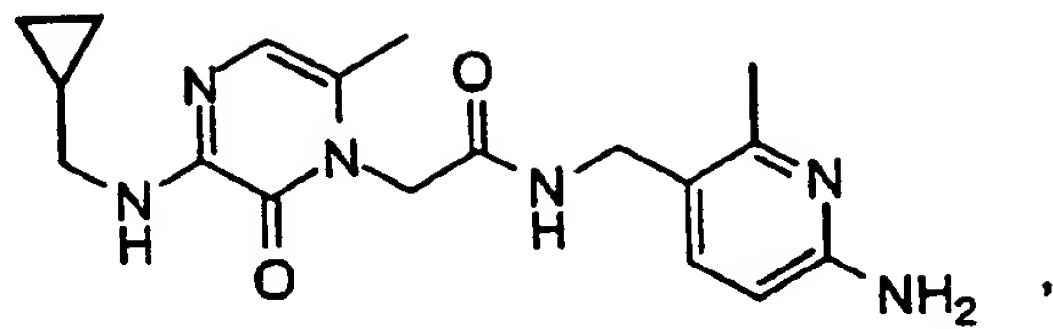
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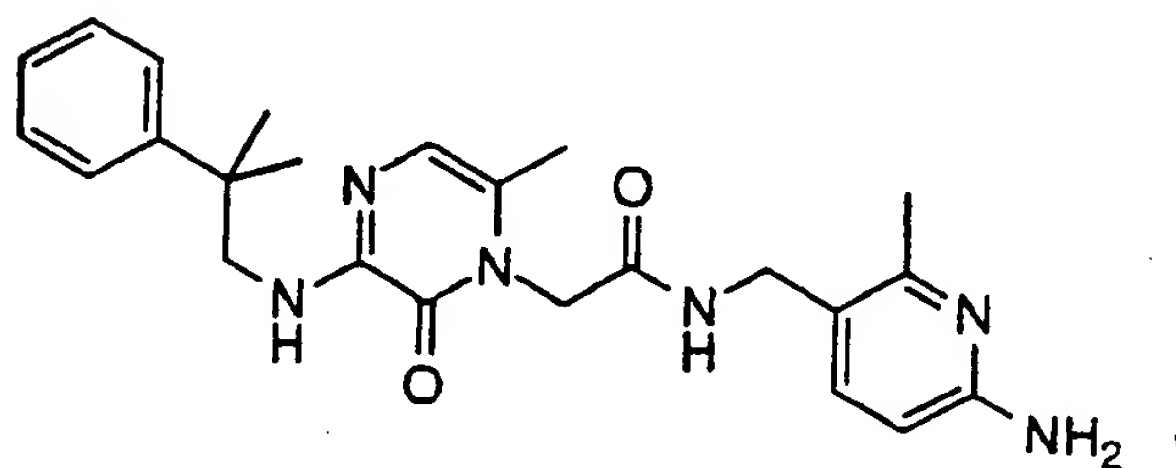
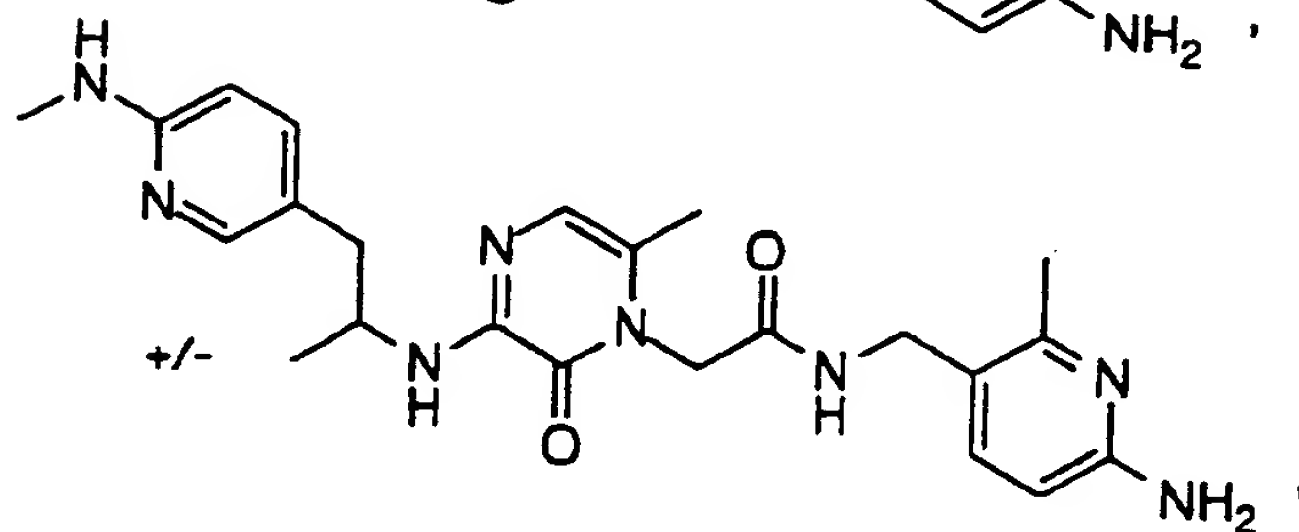
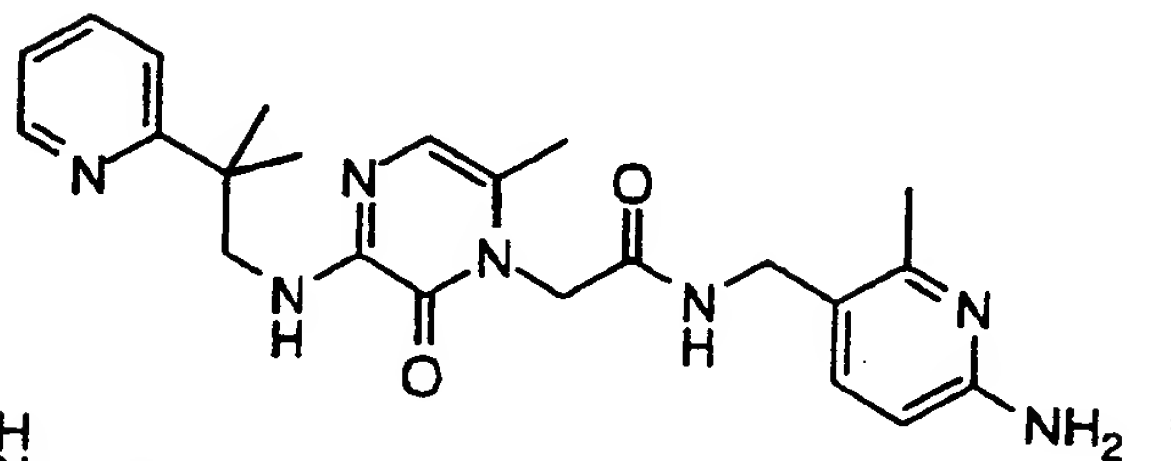
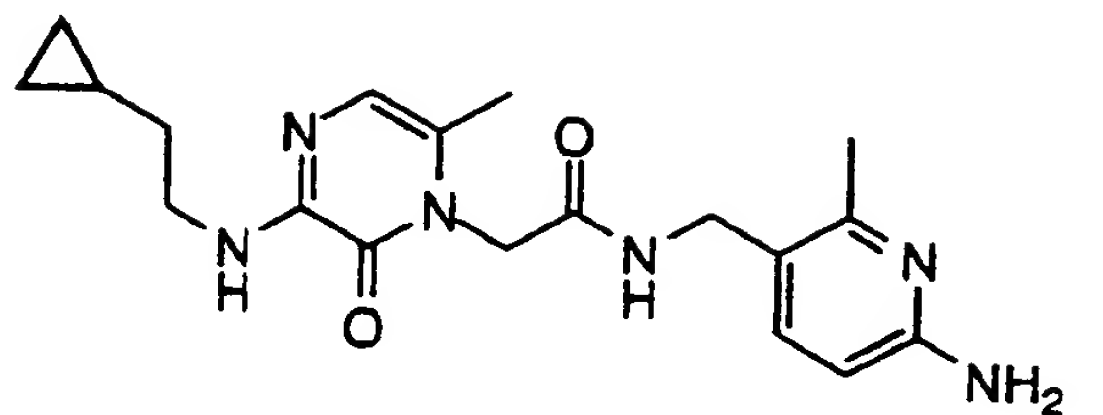
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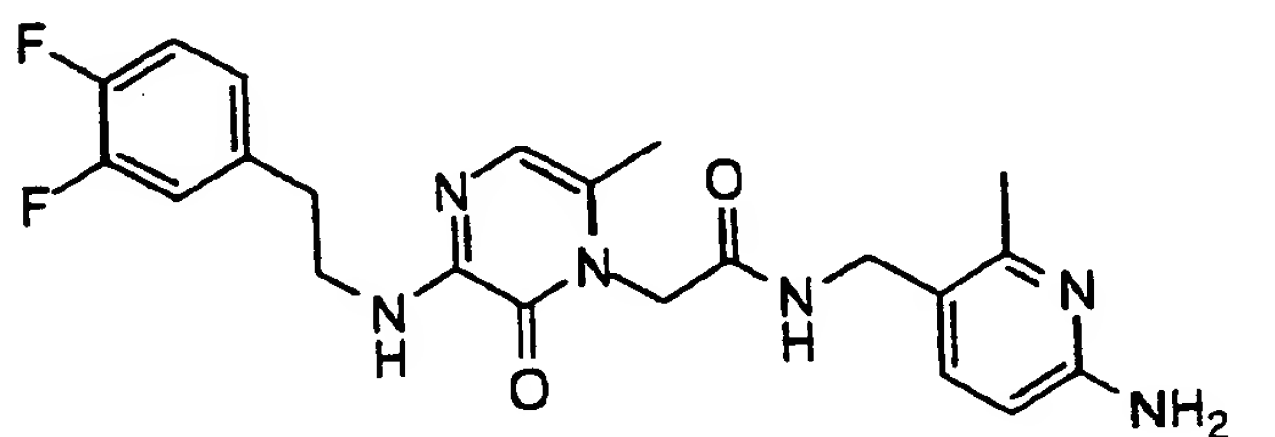
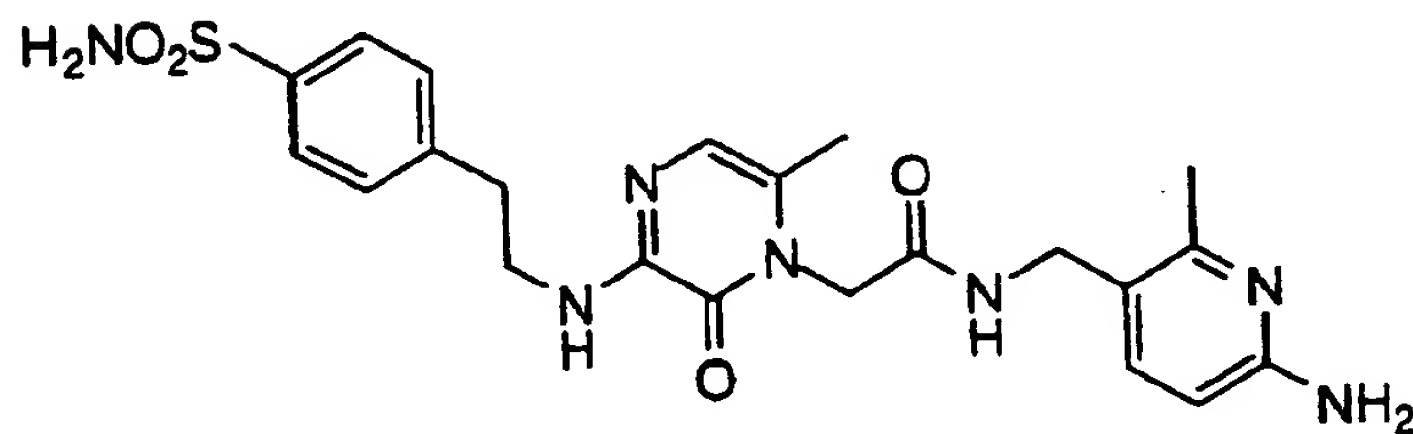
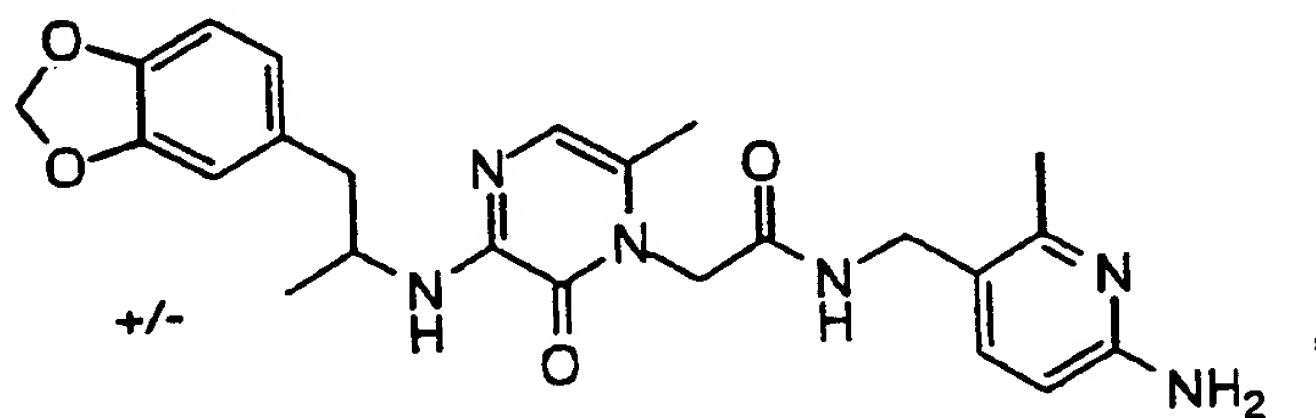
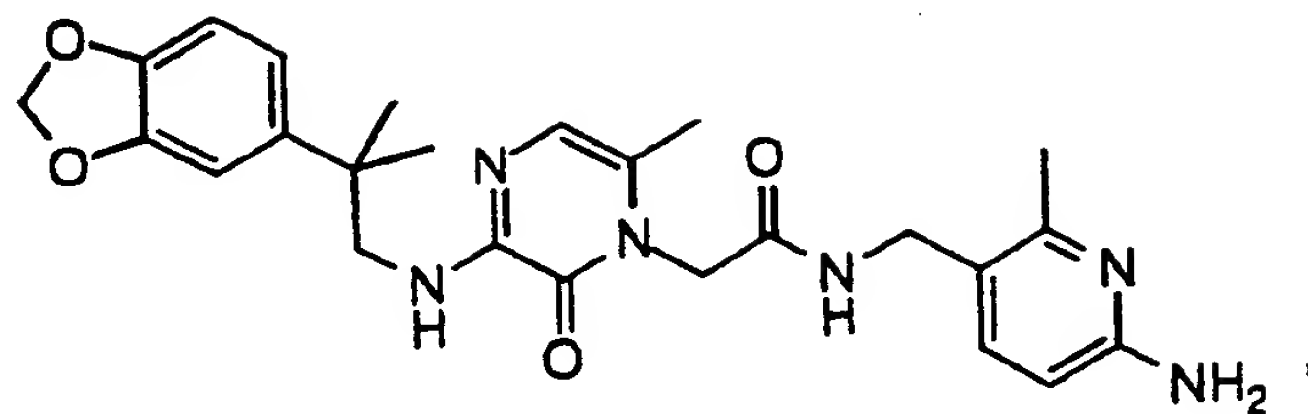
- 172 -



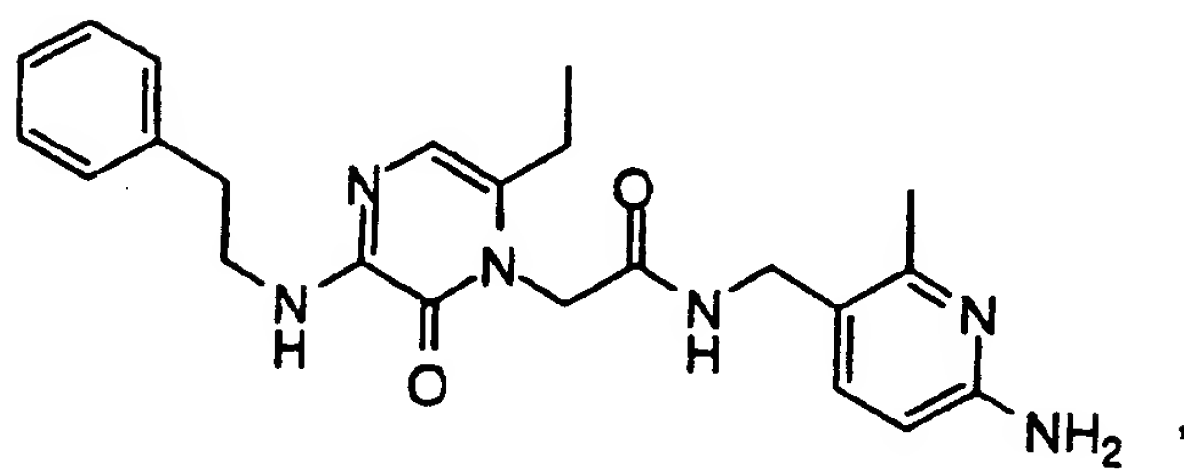
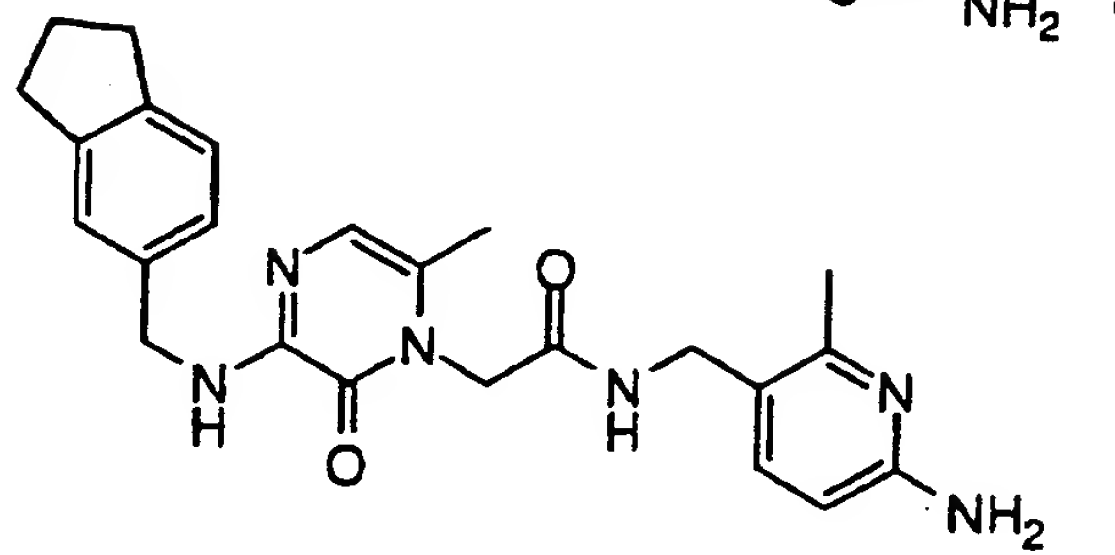
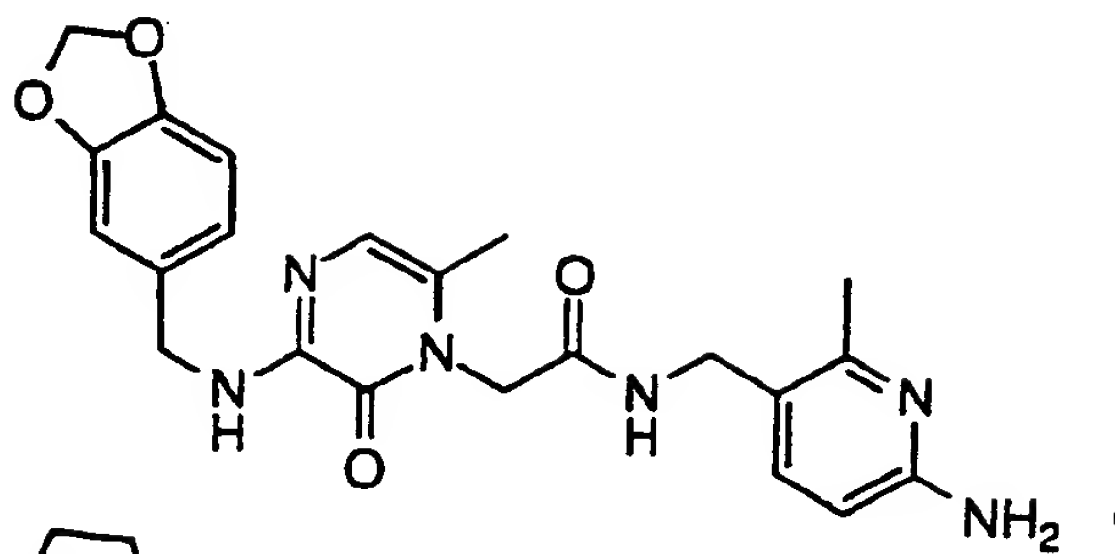
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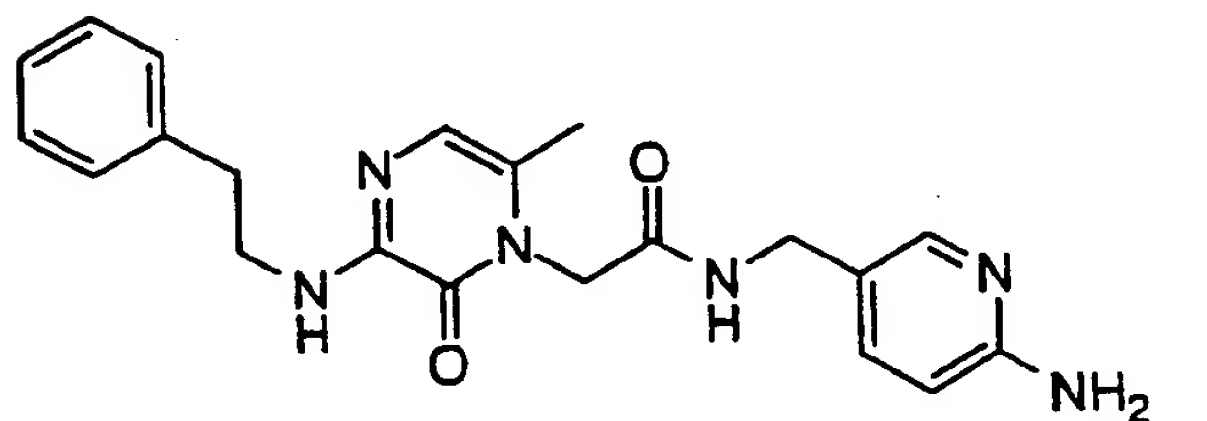
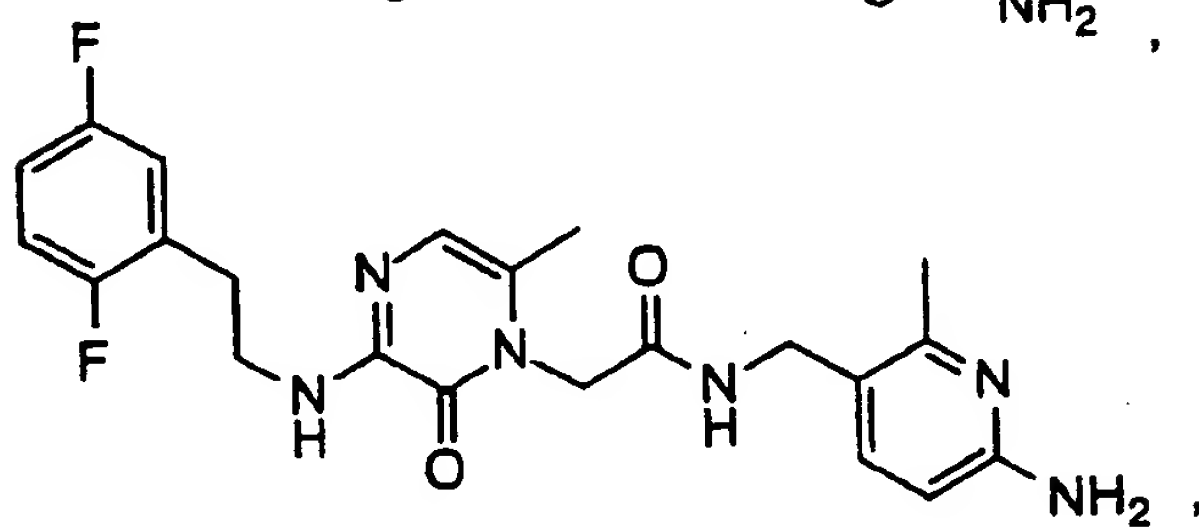
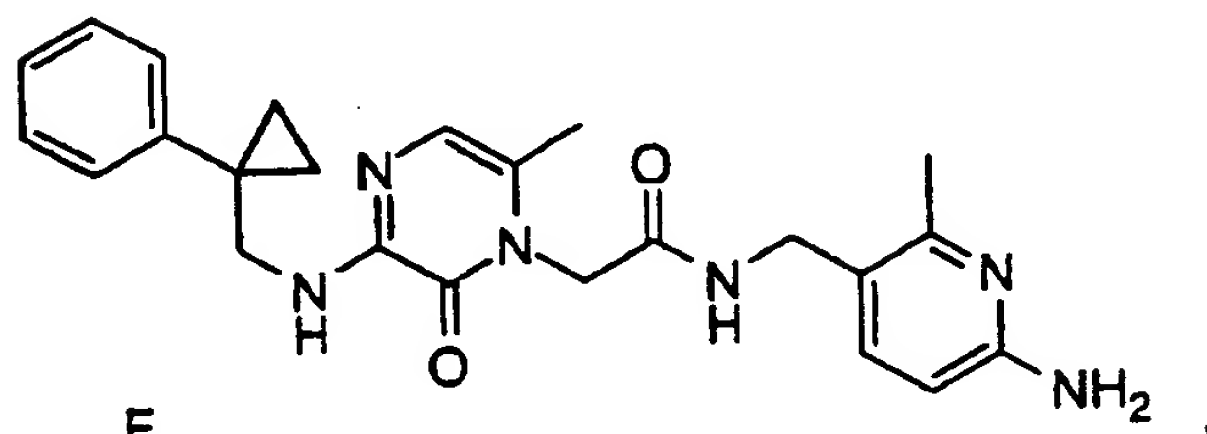
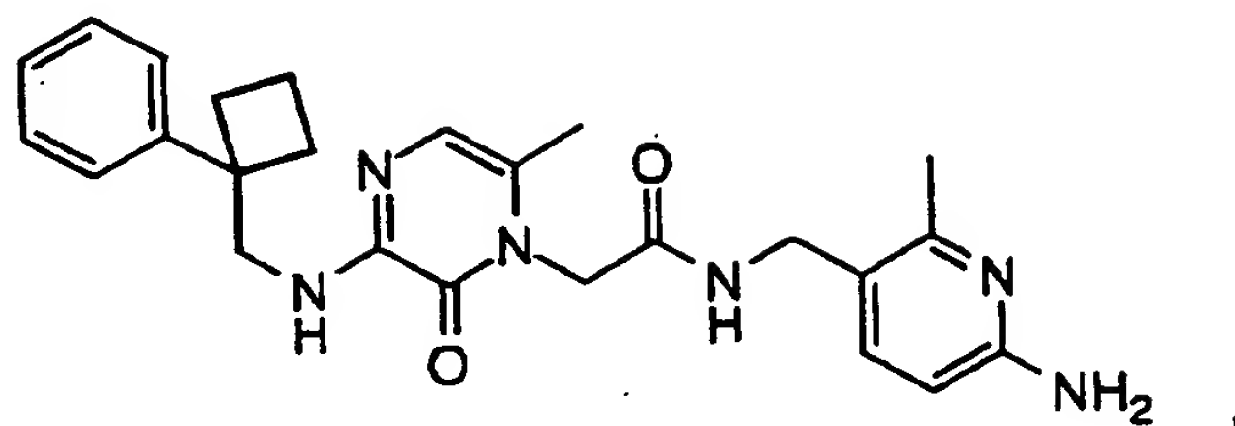
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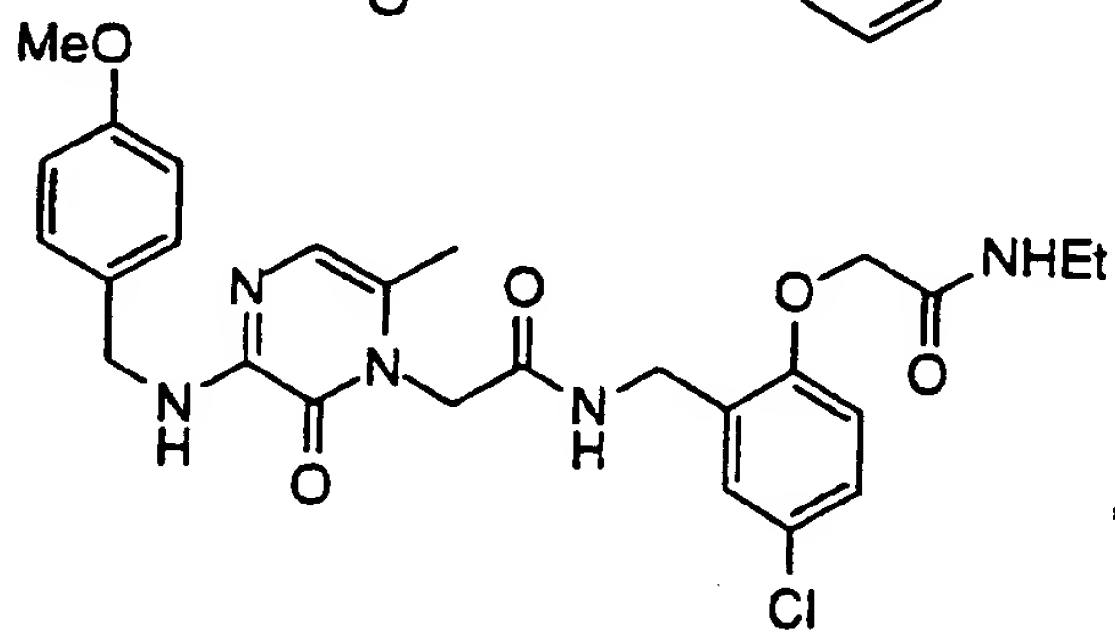
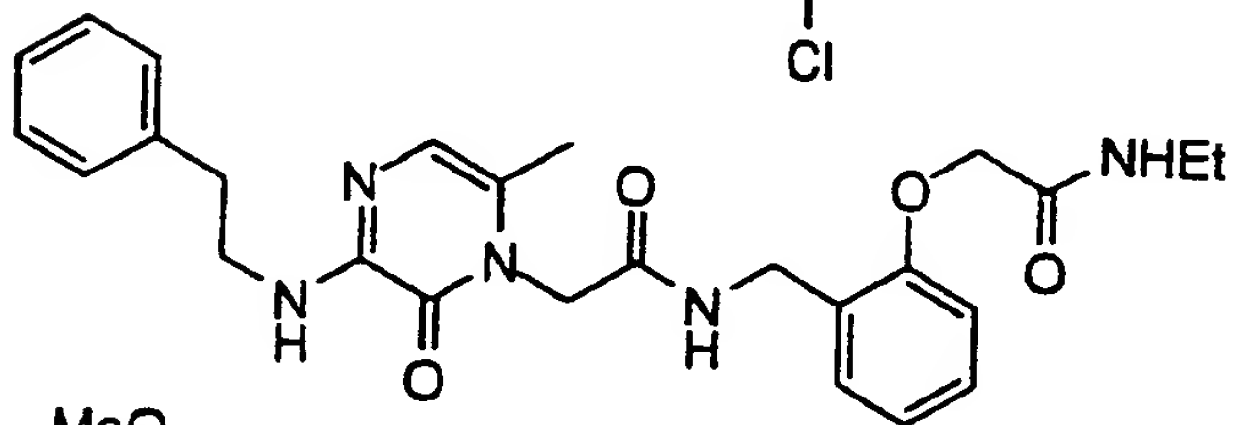
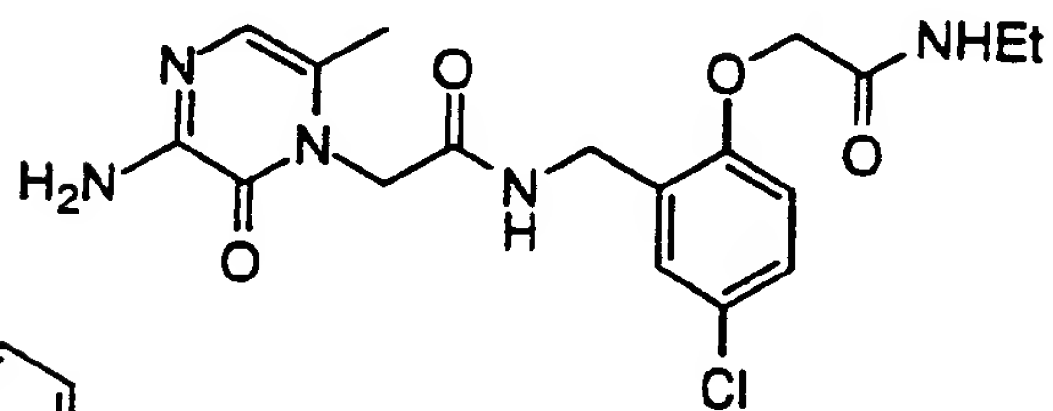
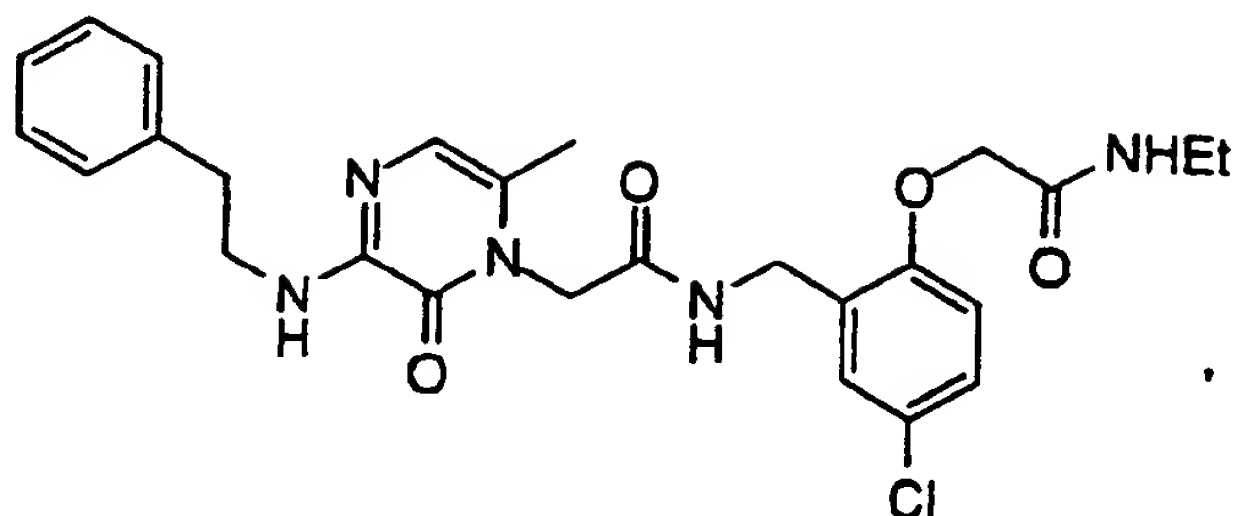
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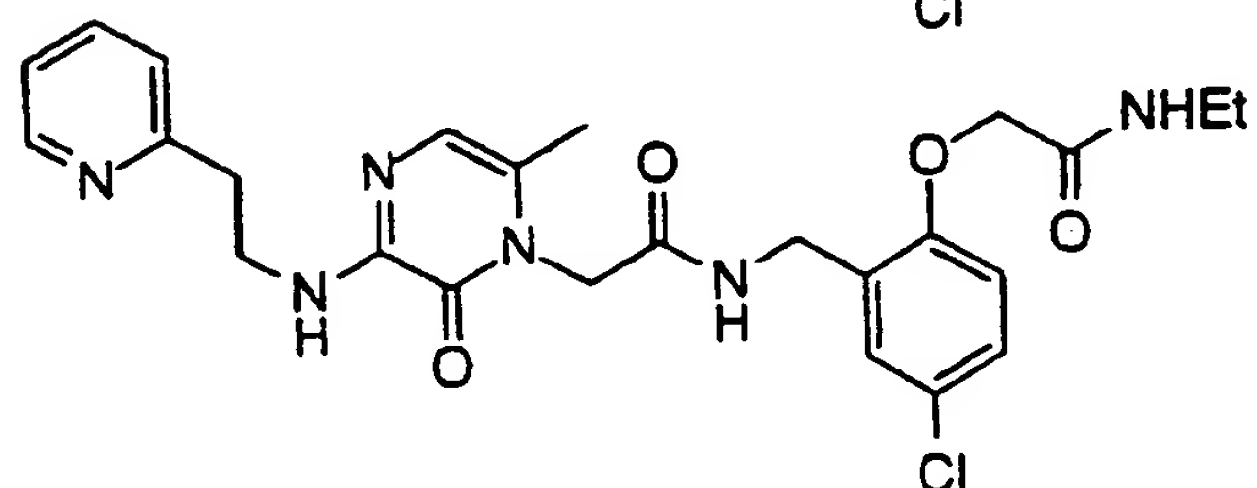
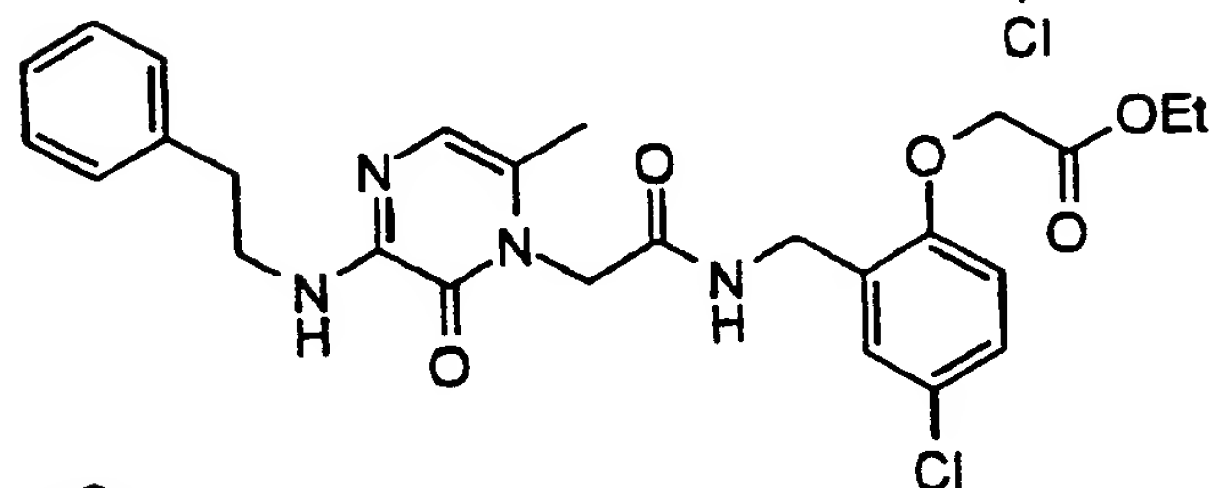
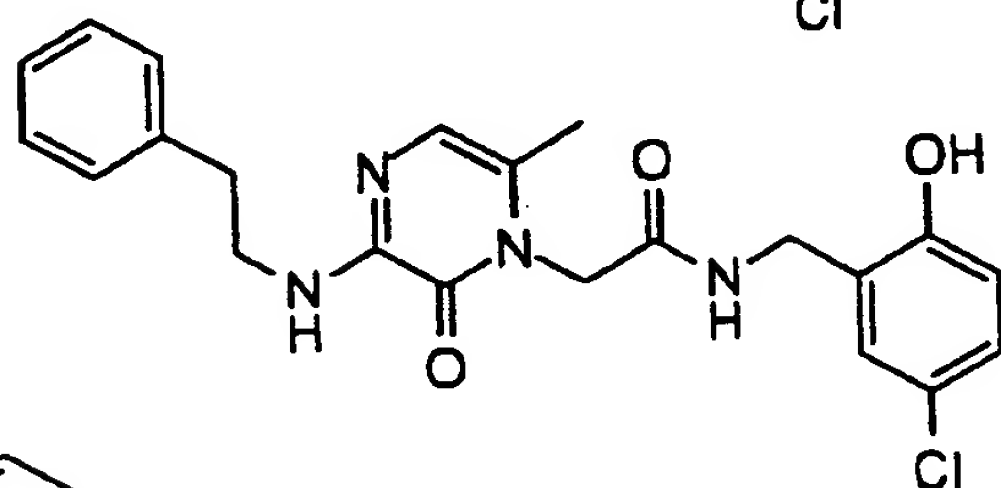
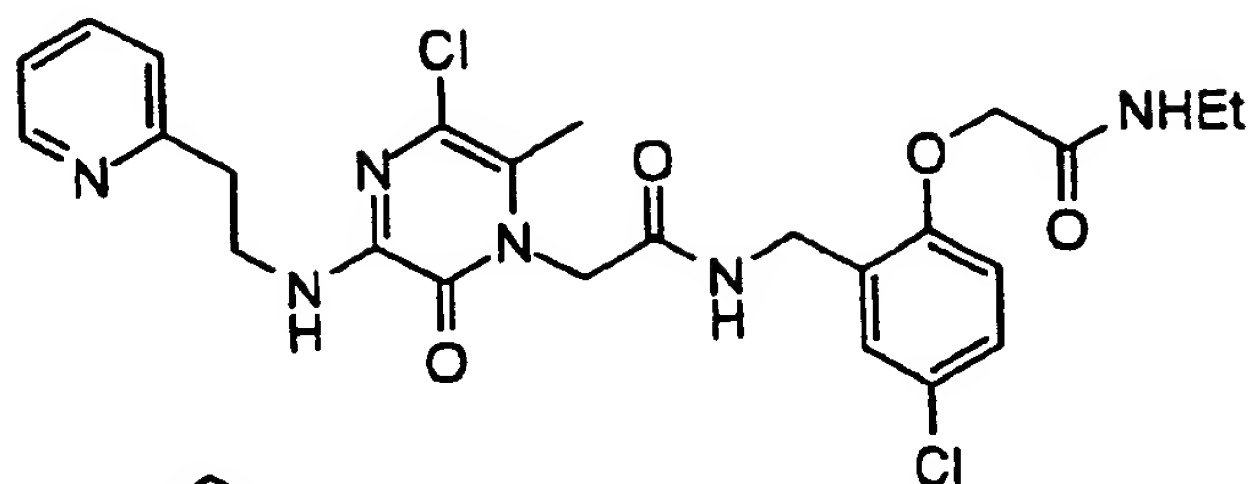
- 176 -



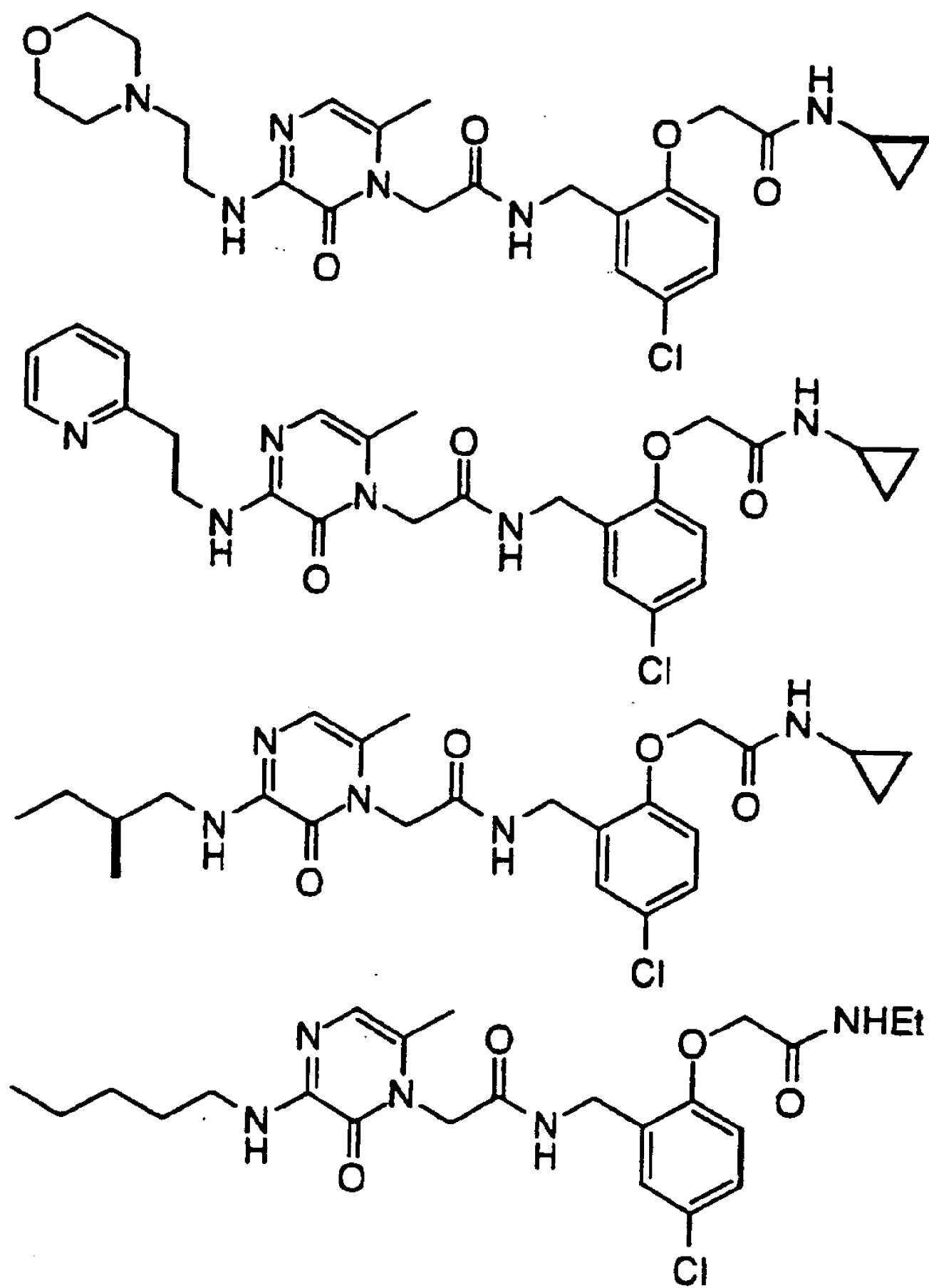
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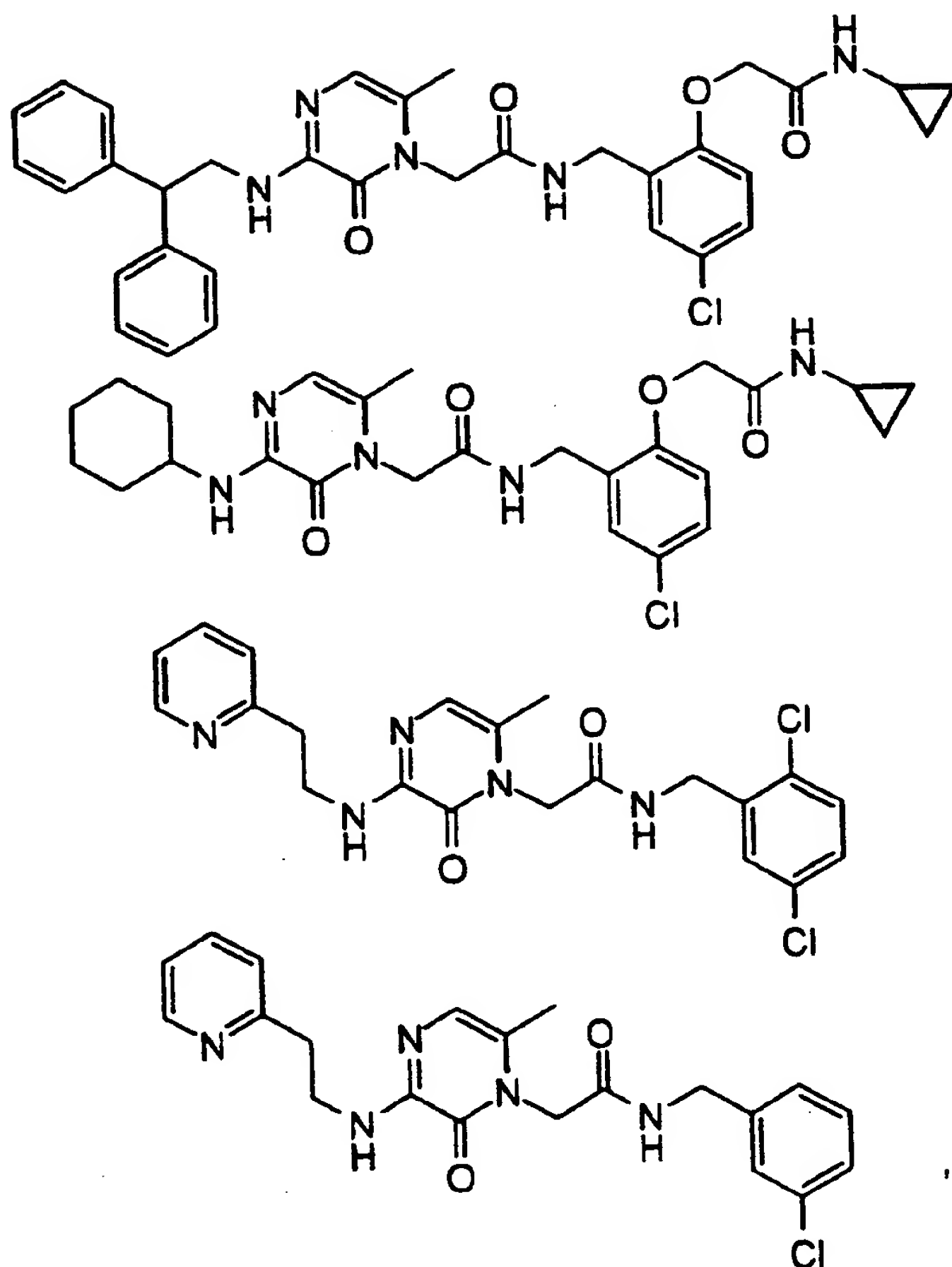
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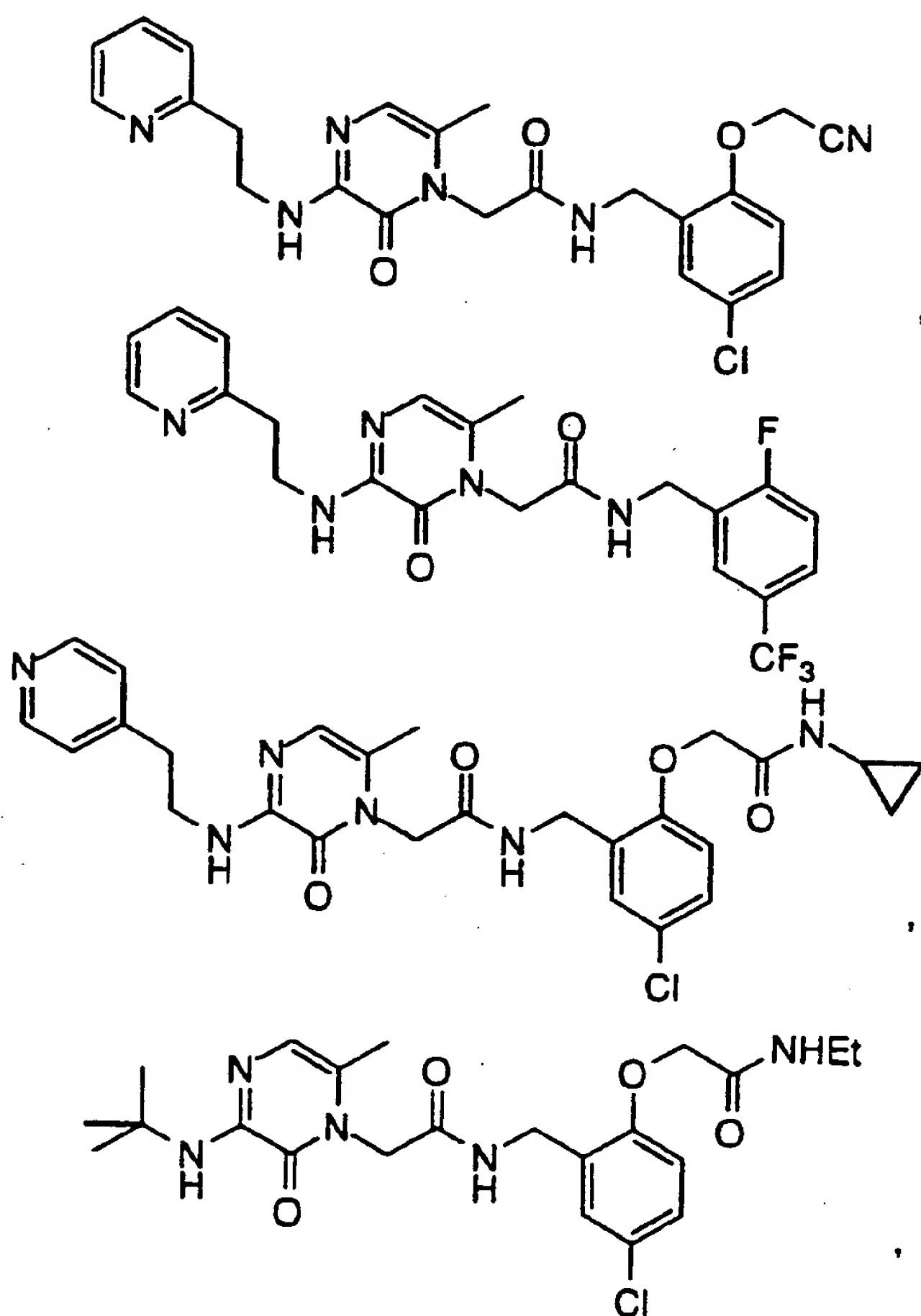
- 179 -



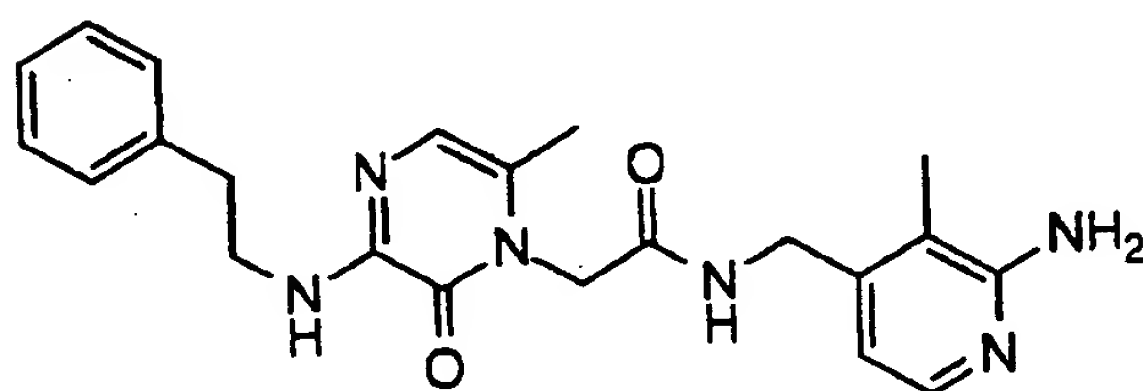
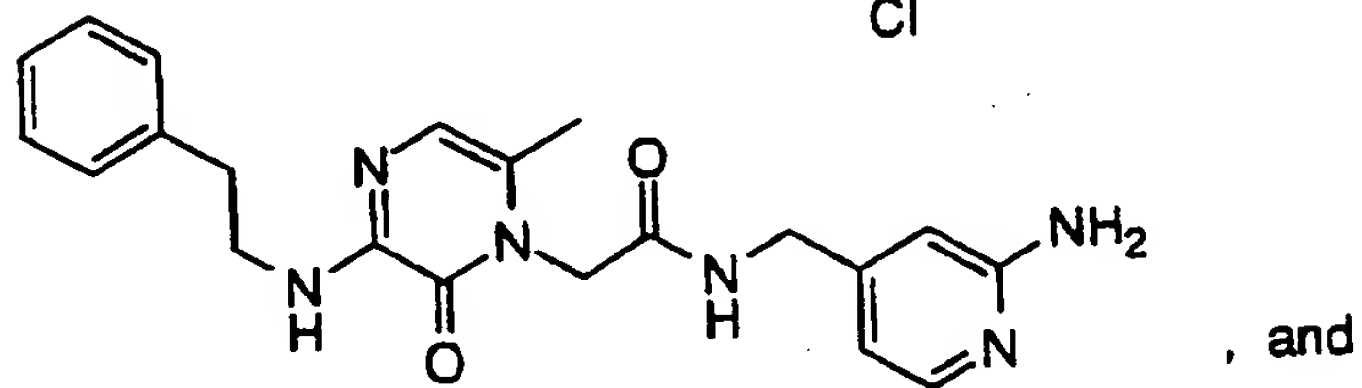
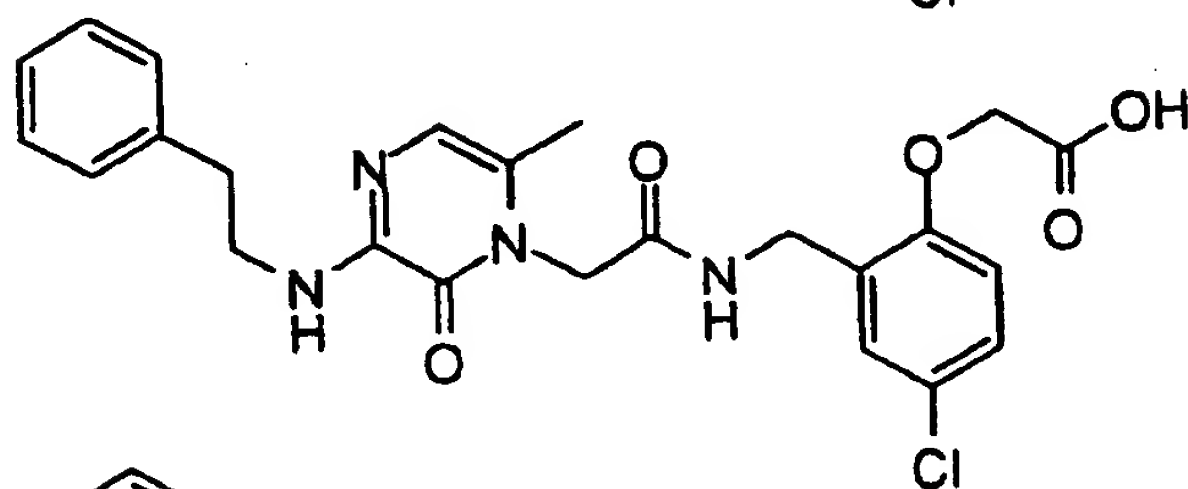
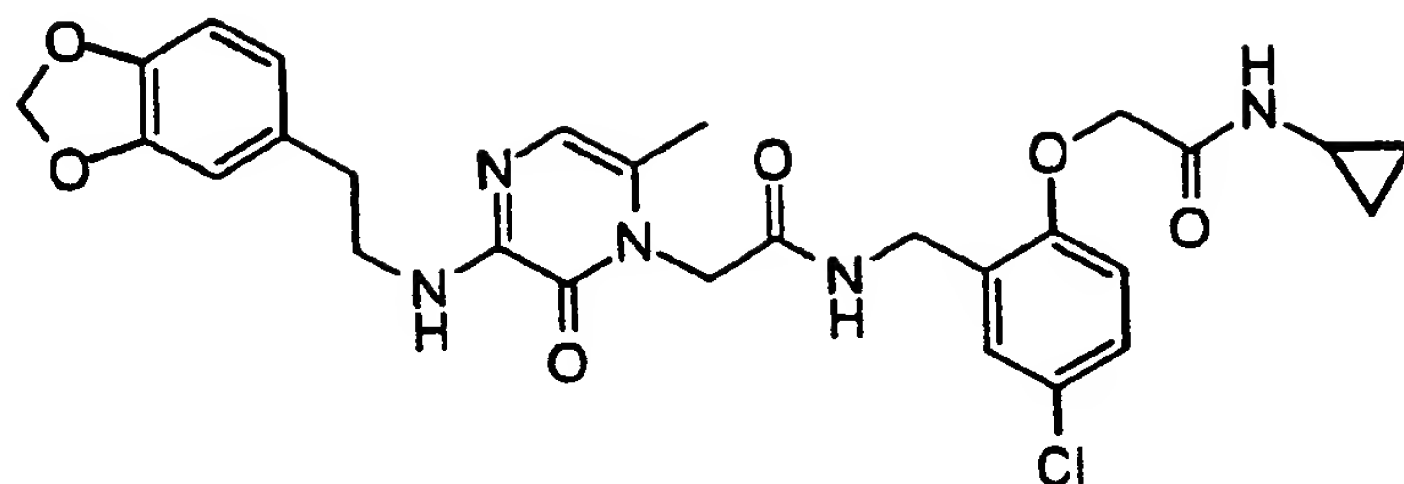
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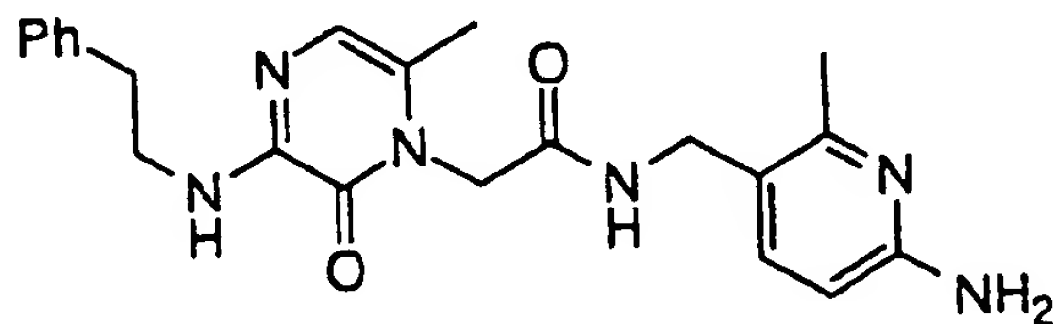
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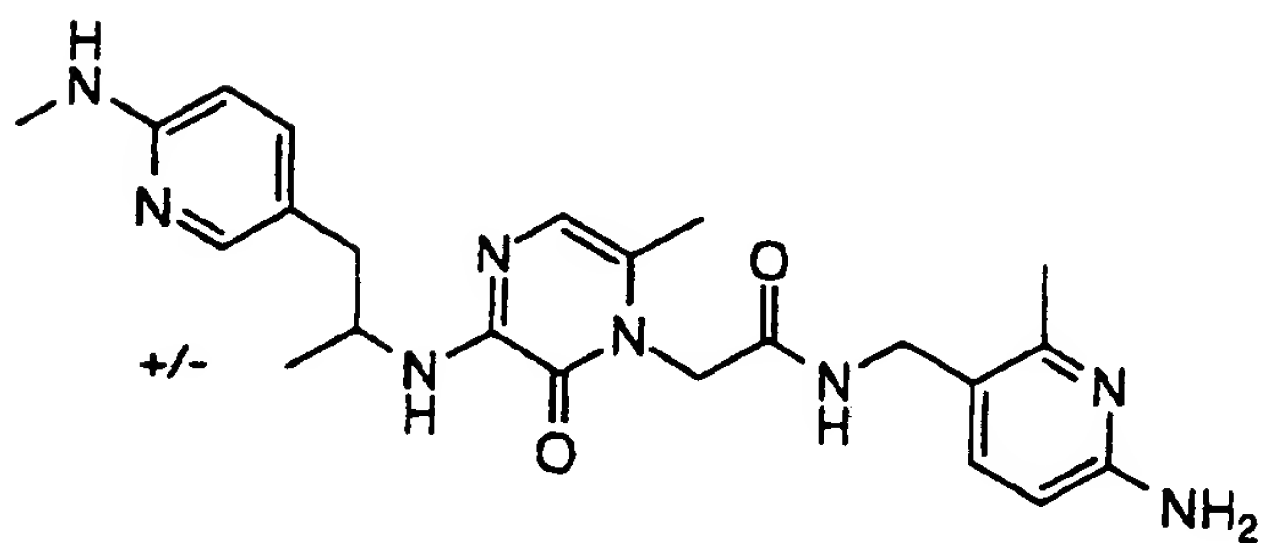
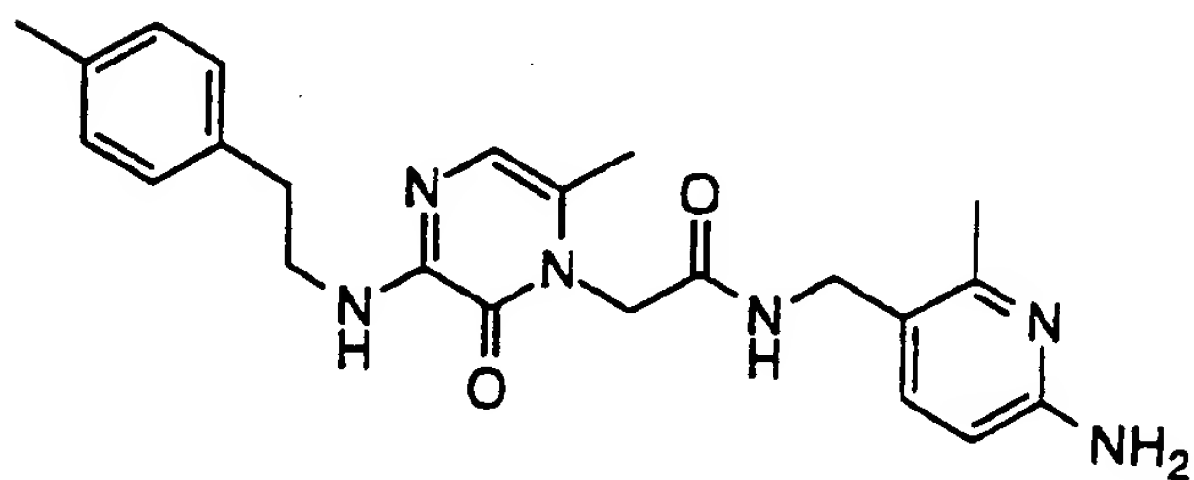
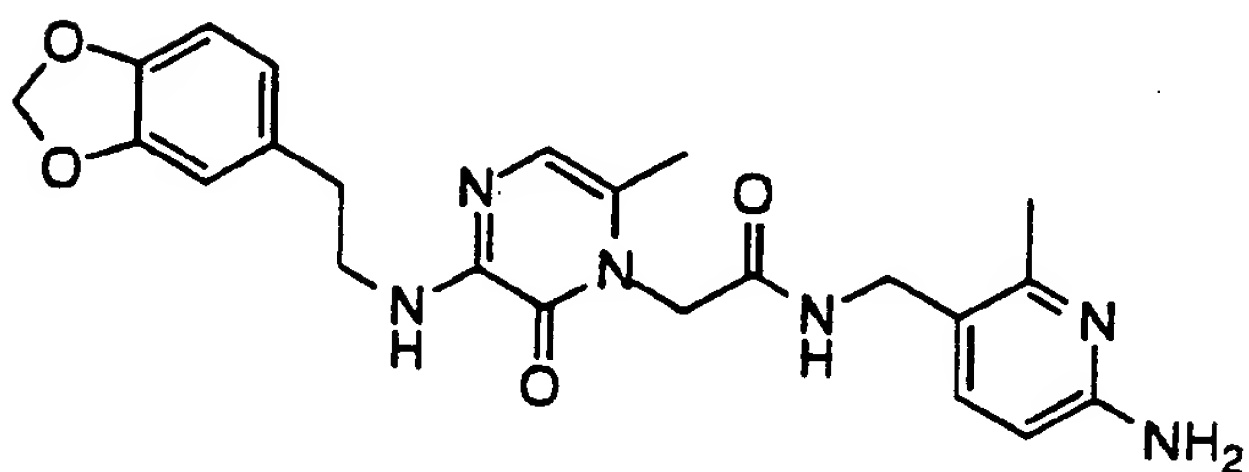
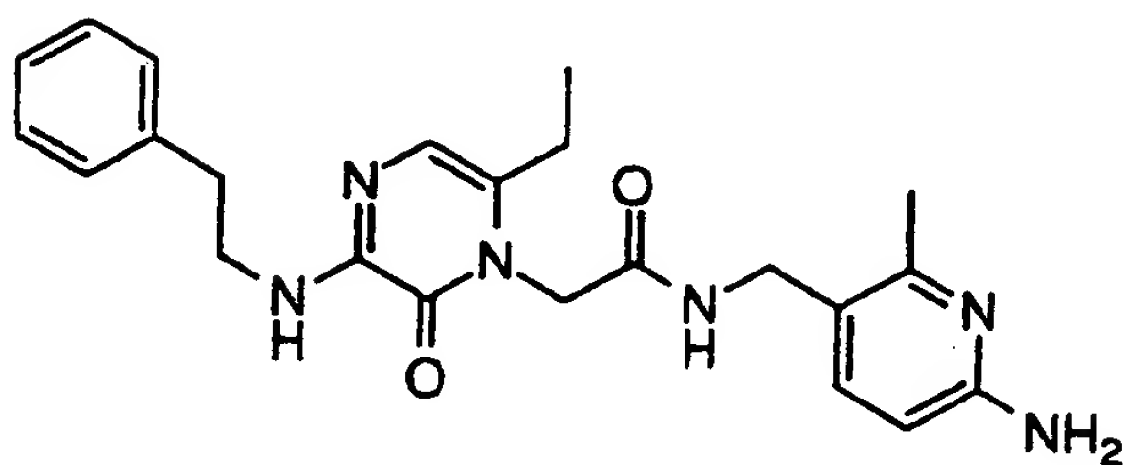
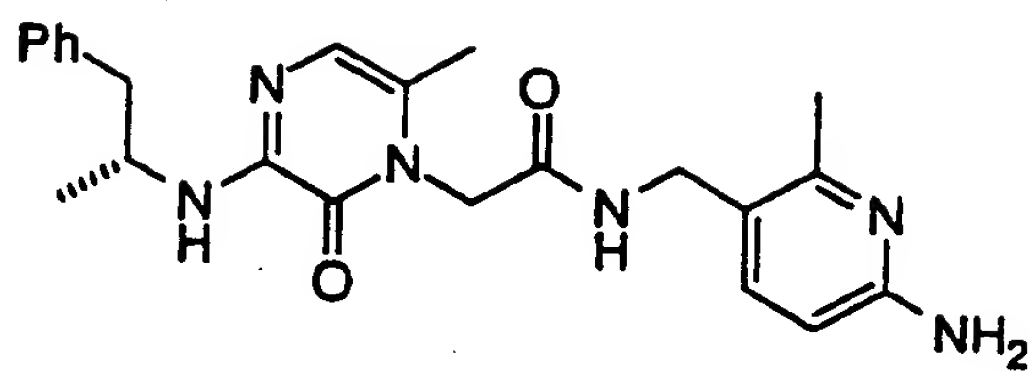
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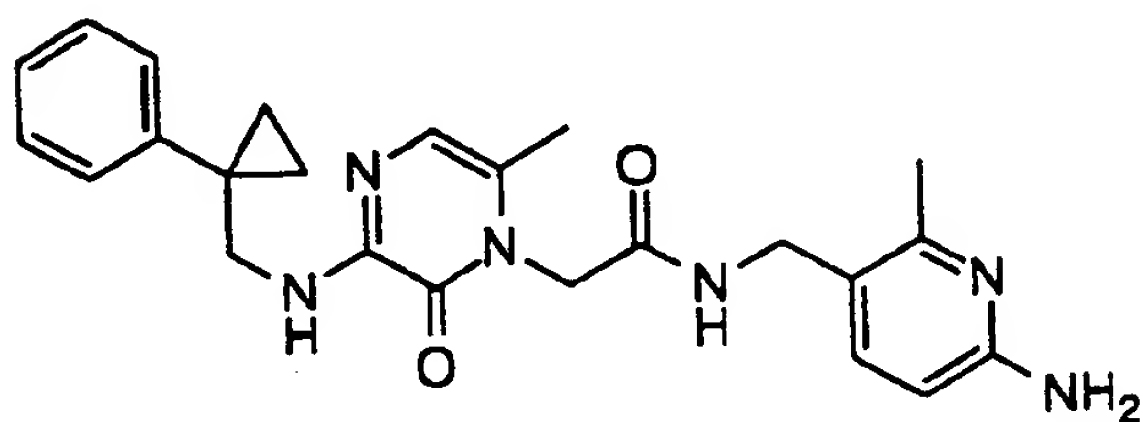
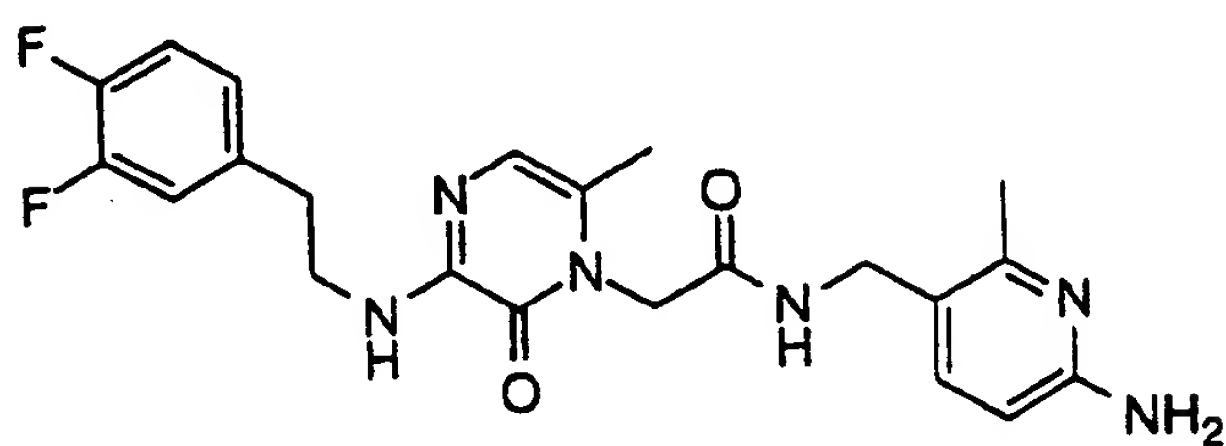
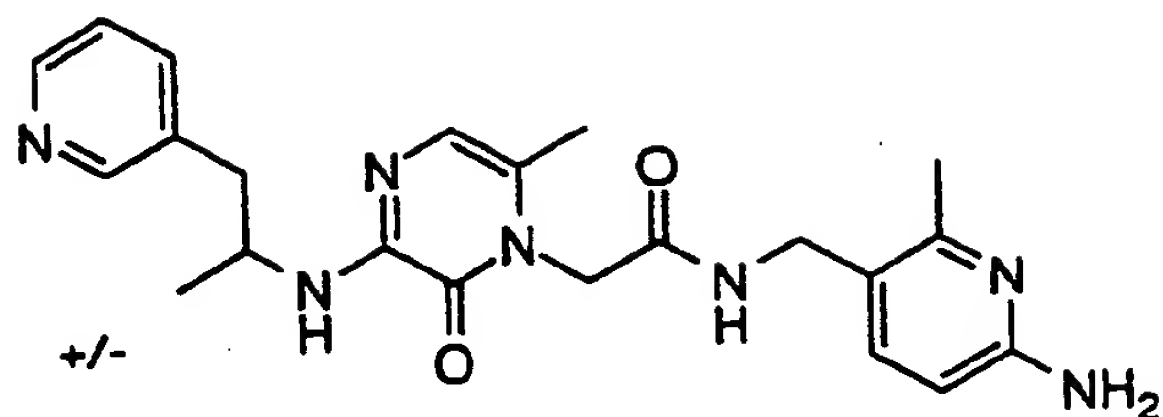
8. The compound of Claim 7, and pharmaceutically acceptable salts thereof, wherein the compound is selected from the group consisting of



- 183 -



- 184 -



- 5 9. The compound of Claim 8, and pharmaceutically acceptable salts thereof, wherein the compound is 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone.
- 10 10. The salt of claim 9 which is 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride.
- 15 11. The salt of claim 10 that exists as polymorphic crystalline form Type A monohydrate.

- 185 -

12. The salt of claim 11 characterized by a differential scanning calorimetry curve, at a heating rate of 5°C/min in an open cup under flowing nitrogen bubbled through water at 5°C, exhibiting an endotherm with an extrapolated onset temperature of about 102°C, a peak temperature of about 112°C and an associated heat of about 115J/gm followed by an endotherm with an extrapolated onset temperature of about 171°C, a peak temperature of about 194°C and an associated heat of about 83J/gm; and an x-ray powder diffraction pattern characterized by spectral d-spacings of 13.06, 12.16, 7.40, 5.71, 4.92, 4.48, 4.40, 3.63, 3.07, 2.98, 2.86 and 2.62Å.

13. A salt of claim 10 that exists as polymorphic crystalline form Type B monohydrate.

14. The salt of claim 13 characterized by a differential scanning calorimetry curve, at a heating rate of 5°C/min in an open cup under flowing nitrogen bubbled through water at 5°C, exhibiting an endotherm with an extrapolated onset temperature of about 120°C, a peak temperature of about 132°C, and an associated heat of about 123J/gm followed by an endotherm with an extrapolated onset temperature of about 160°C, a peak temperature of about 191°C and an associated heat of about 78J/gm; and an x-ray powder diffraction pattern characterized by spectral d-spacings of 12.98, 11.91, 7.24, 5.98, 4.90, 4.46, 4.23, 3.99, 3.75, 3.61, 3.41, 2.94, 2.85 and 2.61Å.

15. A composition for inhibiting thrombus formation in blood comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

16. A method for inhibiting thrombin in blood comprising adding to the blood a composition of Claim 15.

- 186 -

17. A method for inhibiting formation of blood platelet aggregates in blood comprising adding to the blood a composition of Claim 15.

5 18. A method for inhibiting thrombus formation in blood comprising adding to the blood a composition of Claim 15.

10 19. A method for inhibiting thrombus formation in blood comprising adding to the blood a compound of Claim 1 with a fibrinogen receptor antagonist.

15 20. The use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting thrombin, inhibiting thrombus formation, treating thrombus formation, or preventing thrombus formation in a mammal.

20 21. A method for treating or preventing venous thromboembolism and pulmonary embolism in a mammal comprising administering to the mammal a composition of Claim 15.

25 22. A method for treating or preventing deep vein thrombosis in a mammal comprising administering to the mammal a composition of Claim 15.

23. A method for treating or preventing cardiogenic thromboembolism in a mammal comprising administering to the mammal a composition of Claim 15.

30 24. A method for treating or preventing thromboembolic stroke in humans and other mammals comprising administering to the mammal a composition of Claim 15.

- 187 -

25. A method for treating or preventing thrombosis associated with cancer and cancer chemotherapy in a mammal comprising administering to the mammal a composition of Claim 15.

5 26. A method for treating or preventing unstable angina in a mammal comprising administering to the mammal a composition of Claim 15.

10 27. A method for treating or preventing myocardial infarction in a mammal comprising administering to the mammal a composition of Claim 15.

15 28. A method for treating or preventing cardiogenic thromboembolism associated with atrial fibrillation in a mammal comprising administering to the mammal a composition of Claim 15.

20 29. A method for treating or preventing cardiogenic thromboembolism associated with prosthetic heart valves in a mammal comprising administering to the mammal a composition of Claim 15.

30. A method for treating or preventing cardiogenic thromboembolism associated with heart disease in a mammal comprising administering to the mammal a composition of Claim 15.

25 31. A method for treating or preventing atherosclerosis in a mammal comprising administering to the mammal a composition of Claim 15.

30 32. A method for treating or preventing thrombosis in a mammal with inherited thrombophilic diseases such as Protein C deficiency, Protein S deficiency, antithrombin III and factor V Leiden comprising administering to the mammal a composition of Claim 15.

- 188 -

33. A method for treating or preventing thrombosis in a mammal with acquired thrombophilic disorders such as systemic lupus erythematosus comprising administering to the mammal a composition of Claim 15.

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34. A method for treating or preventing ischemic heart disease in a mammal comprising administering to the mammal a composition of Claim 15.

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35. A method for lowering the propensity of a device which contacts blood to clot blood which comprises coating the device with a composition of claim 15.

15 36. A method for treating or preventing reocclusion in a mammal during or following percutaneous transluminal coronary angioplasty comprising administering to the mammal a composition of Claim 15.

20 37. A method for treating or preventing restenosis in a mammal following percutaneous transluminal coronary angioplasty comprising administering to the mammal a composition of Claim 15.

25 38. A method for treating or preventing occlusion of coronary artery bypass grafts in a mammal comprising administering to the mammal a composition of Claim 15.

30 39. A method for treating or preventing occlusive cerebrovascular disease in a mammal comprising administering to the mammal a composition of Claim 15.

40. A method for maintaining patency in arteriovenous cannulas inserted in a mammal comprising administering to the mammal a composition of Claim 15.

- 189 -

41. A method for maintaining patency of indwelling catheters in a mammal comprising administering to the mammal a composition of Claim 15.

5 42 A process for producing 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride Type A monohydrate comprising the steps of:

- 10 a) dissolving 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone in acetic acid solvent and adding aqueous HCl;
 b) recovering the resultant solid phase; and
 c) removing the solvent therefrom.

15 43. A process of claim 42 wherein the amount of aqueous HCl is such that the final water content in the acetic acid is between 1 and 5 weight %.

20 44 A process for producing 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone dihydrochloride Type B monohydrate comprising the steps of:

- 25 a) dissolving 3-(2-Phenethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylcarboxamidomethylpyridinyl)-pyrazinone in hydrochloric acid solvent;
 b) recovering the resultant solid phase; and
 c) removing the solvent therefrom.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/06744

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D241/20 C07D401/12 C07D405/14 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 262 096 A (CIBA-GEIGY) 30 March 1988 see claims; tables 1-6,14 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

7 August 1997

Date of mailing of the international search report

18.08.97

Name and mailing address of the ISA

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Francois, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/06744 -

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 21-34, 36-39
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/06744 -

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 262096 A	30-03-88	AU 593945 B	22-02-90
		AU 7897787 A	31-03-88
		CA 1292738 A	03-12-91
		DE 3775686 A	13-02-92
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